

Gatifloxacin Found Safe, Effective for Otitis Media

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Gatifloxacin appears to be both safe and highly effective in treating acute and recurrent otitis media in children, and is not associated with either acute or long-term joint disorders, Michael Pichichero, M.D., and his colleagues reported.

In the compilation of four clinical trials (two phase II and two phase III), they

also concluded that the drug, a fluoroquinolone, was more effective in eradicating middle-ear pathogens than was amoxicillin/clavulanate.

The effect of a 10-day course of gatifloxacin (10 mg/kg per day) was evaluated in 867 children aged 6 months to 7 years. The phase III trials also included 309 children who received amoxicillin/clavulanate as a comparator.

All children had acute otitis media (OM), recurrent OM, or OM treatment

failure (Clin. Infect. Dis. 2005;41:470-8).

In the phase II trials (414 children), the high rate of discontinuation (8%) was primarily due to vomiting because of the bitter taste of an early formulation of the drug, said Dr. Pichichero of the University of Rochester (N.Y.) and his coinvestigators. In the phase III studies, with a new formulation, the rate of discontinuation was similar in both groups (2%).

Transient arthralgia occurred in 12 (1.4%) of the 867 children. There were no

abnormal imaging studies in any of the 7 who were examined by an orthopedist. One child discontinued therapy due to knee swelling and abnormal gait; no joint abnormalities were seen on imaging.

In the phase III studies, the rate of arthralgia was similar between the gatifloxacin and amoxicillin/clavulanate groups (1.5% and 1.3%).

One-year safety data were available for 671 gatifloxacin-treated children. There was no evidence of arthropathy in any. A 4-year-old girl treated with the study drug developed Achilles tendon pain, which resolved in 5 days with rest and ice.

Gatifloxacin was not associated with hepatotoxicity, clinically relevant hypoglycemia, phototoxicity, or central nervous system toxicity.

The cure rate of the pooled phase II studies was 81%. In the first phase III study, the cure rate of gatifloxacin was 90%, compared with 84% for amoxicillin/clavulanate.

The cure rate for gatifloxacin in the second phase II study was 85%, compared with 79% for amoxicillin/clavulanate.

The study drug was especially effective in children younger than 2 years with severe acute otitis media; the cure rate was 90%, compared with 75% for the amoxicillin regimen. Gatifloxacin eradicated both *Streptococcus pneumoniae* and *Haemophilus influenzae*. It achieved highly significant clinical cure rates for pathogens that were resistant to one or two other antibiotics.

Pediatric use of gatifloxacin remains controversial, not only because of concerns about arthropathy, but also because childhood resistance could impact the drug's usefulness in future adult populations, the authors noted.

However, in an accompanying editorial, Colin Marchant, M.D., said the drug deserves a chance.

Promising trial results, scheduled for discussion at a May 2004 meeting of the Food and Drug Administration's Anti-Infective Drugs Advisory Committee, were scrapped at the last minute when Bristol-Myers Squibb, the drug's manufacturer, abruptly withdrew its new drug application. The stated reason was that the drug company and the FDA could not agree on a risk-management program for the drug, said Dr. Marchant of the Boston Medical Center (Clin. Infect. Dis. 2005;41:479-80).

"The safety data on gatifloxacin use in children should be reviewed in a public forum [such as the committee]," he said. "If there are no data indicating increased risks of side effects with gatifloxacin ... then recommendations for further safety studies should be put forward; and the nature and basis for a risk-management program should also be exposed to public scrutiny and discussion."

Brief Summary of Prescribing Information

OMACOR® (omega-3-acid ethyl esters) Capsules

DESCRIPTION

Omacor, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Omacor (omega-3-acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).

CLINICAL STUDIES

The effects of Omacor 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Omacor, 42 on placebo) with very high triglyceride levels (Table 1). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.

Table 1. Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥500 mg/dL)

	TG		LDL-C		CHOL		HDL-C		VLDL-C		non-HDL-C	
	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg
Placebo	788	+6.7	108	-4.8	314	-1.7	24	0.0	175	-0.9	292	-3.6
Omacor 4g/day	816	-44.9	89	+44.5	296	-9.7	22	+9.1	175	-41.7	271	-13.8
Difference		-51.6		+49.3		-8.0		+9.1		-40.8		-10.2

BL = Baseline (mg/dL); % Chg = Percent Change from Baseline; Difference = Omacor - Placebo

Omacor 4 g per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Omacor treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively. The effect of Omacor on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of Omacor on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined.

INDICATIONS AND USAGE

Omacor is indicated as an adjunct to diet to reduce very high (≥500 mg/dL) triglyceride (TG) levels in adult patients.

Usage Considerations

According to accepted clinical guidelines, excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia (HTG) and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy for HTG. The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet. (See PRECAUTIONS).

CONTRAINDICATIONS

Omacor is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General

Initial Therapy

Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Omacor therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG-lowering drug therapy.

Continued Therapy

Laboratory studies should be performed periodically to measure the patient's TG levels during Omacor therapy. Omacor therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

Information for Patients

Omacor should be used with caution in patients with known sensitivity or allergy to fish.

Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

Laboratory Tests

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Omacor therapy. In some patients, Omacor increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Omacor therapy.

Drug Interactions

Anticoagulants

Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Omacor and concomitant anticoagulants. Patients receiving treatment with both Omacor and anticoagulants should be monitored periodically.

Cytochrome P450-Dependent Monooxygenase Activities

Omega-3-fatty acid containing products have been shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Omacor to induce P450 activities in humans has not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. It is unknown whether Omacor can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Omacor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison. In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000 mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

OMACOR® (omega-3-acid ethyl esters) Capsules

Nursing Mothers

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Omacor is administered to a woman who is breastfeeding.

Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use

A limited number of patients over 65 years of age were enrolled in the clinical studies. In the pooled analyses, safety and efficacy findings in subjects over 60 years of age (approximately 25% of the study population) did not appear to differ from those of subjects less than 60 years of age.

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with Omacor 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 2. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Omacor and 2.6% of patients treated with placebo.

Table 2. Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Hypertriglyceridemia That Used Omacor 4 g per Day

BODY SYSTEM Adverse Event	Omacor (N = 226)		Placebo* (N = 228)	
	n	%	n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Eructation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.

*Placebo was corn oil for all studies.

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:

BODY AS A WHOLE: enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, sudden death, and viral infection.
CARDIOVASCULAR SYSTEM: arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.
DIGESTIVE SYSTEM: anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.
HEMATOLOGIC-LYMPHATIC SYSTEM: lymphadenopathy.
METABOLIC AND NUTRITIONAL DISORDERS: edema, hyperglycemia, increased ALT, and increased AST.
MUSCULOSKELETAL SYSTEM: arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.
NERVOUS SYSTEM: central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.
RESPIRATORY SYSTEM: asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.
SKIN: alopecia, eczema, pruritis, and sweating.
SPECIAL SENSES: cataract.
UROGENITAL SYSTEM: cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DRUG ABUSE AND DEPENDENCE

Omacor does not have any known drug abuse or withdrawal effects.

OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving Omacor, and should continue this diet during treatment with Omacor. In clinical studies, Omacor was administered with meals.

The daily dose of Omacor is 4 g per day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).

HOW SUPPLIED

Omacor (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation OMACOR in bottles of 120 (NDC 65726-424-27).

Recommended Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not freeze. Keep out of reach of children.

Rx only

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