

WORST PILLS



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BEST PILLS

N E W S

SIDNEY M. WOLFE, M.D., EDITOR

December 2004 ♦ VOL. 10, NO. 12

DO NOT USE UNTIL — OCTOBER 2009 Zetia (Ezetimibe) Or Vytorin (Ezetimibe with Simvastatin) For Cholesterol Lowering

The Food and Drug Administration (FDA) approved Zetia (ezetimibe) in October 2002 to manage high cholesterol. It was approved to be used either alone or in combination with the widely used family of cholesterol lowering agents known as “statins.” More recently, in July of 2004, FDA approved a single combination pill of Vytorin (ezetimibe and simvastatin). Zetia alone has rapidly moved on to the list of top-selling drugs with more than 4.2 million prescriptions being dispensed in 2003 in U.S. pharmacies.

Zetia works to lower cholesterol in a new way different from the

statins: it inhibits the absorption of cholesterol in the small intestine, whereas the statins work by blocking cholesterol production in the liver. Drugs that work in new ways are always a cause for concern

because they have the potential to cause adverse drug reactions in unexpected new ways. That is a particular worry in this case, since clinical trials were so short (only 3

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The Health Research Group's Seven Year Rule

You should wait at least seven years from the date of release to take any new drug unless it is one of those rare “breakthrough” drugs that offers you a documented therapeutic advantage over older proven drugs. New drugs are tested in a relatively small number of people before being released, and serious adverse effects or life-threatening drug interactions may not be detected until the new drug has been taken by hundreds of thousands of people. A number of new drugs have been withdrawn within their first seven years after release. Also, warnings about serious new adverse reactions have been added to the labeling of a number of drugs, or new drug interactions have been detected, usually within the first seven years after a drug's release.

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months vs. the more usual 6 to 12 months, or longer).

The statins on the market in the U.S. which can be combined with Zetia, are Lipitor (atorvastatin), Lescol (fluvastatin), Mevacor (lovastatin), Pravachol (pravastatin), Crestor (rosuvastatin), and Zocor (simvastatin). Baycol (cerivastatin) was withdrawn from the market in August 2001 because it produced rhabdomyolysis, a condition causing rapid muscle breakdown that can result in kidney failure and death (see *Worst Pills, Best Pills News* October 2001). The Health Research Group has asked the FDA to remove Crestor from the market.

Both Zetia and the fixed combination with simvastatin are co-promoted by Schering-Plough and Merck. The companies' principle marketing claim for Zetia has been improved safety over other cholesterol lowering drugs, particularly the statins, but with no actual proof that safety is, in fact, improved. Indeed, there is already evidence from the FDA Adverse Events Reports System (AERS) that Zetia may, on its own, cause rhabdomyolysis.

Much of this article is based on publicly available FDA reviews of clinical trials and pharmacology studies that ezetimibe's manufacturer submitted to support the approval of the drug. We find these reviews invaluable as the analyses are independent of company influence, unlike so much of the peer reviewed medical literature. These reviews can be found on FDA's website for approved products: www.accessdata.fda.gov/scripts/

Any person with elevated LDL cholesterol or other form of elevated blood fats (hyperlipidemia) should undergo medical evaluation to rule out other causes before drug treatment is begun.

Secondary causes are:

Diabetes

Hypothyroidism (low thyroid)

Chronic kidney failure

Drugs that increase LDL cholesterol and decrease HDL cholesterol are progestins, anabolic steroids, and corticosteroids.

[cdcr/drugsatfda/index.cfm](http://cdcr.drugsatfda/index.cfm).

We are concerned about any new drug but are particularly concerned about the use of Zetia together with statins. The FDA subsequently approved the fixed combination pill of Vytorin (ezetimibe and simvastatin). This approval occurred despite the fact that the FDA Pharmacology Reviewer sounded a warning of serious safety concerns about the combination, and recommended *against* approval. She observed that no matter how small the amount of the two drugs administered together to laboratory animals, toxicity was still seen; that is, there was no "no-observed-adverse-effect-level" or NOAEL. The technical definition of NOAEL is that it is the highest concentration of a substance which causes no detectable adverse change in morphology, functional capacity, growth, development, or life span (of laboratory animals, in this case).

Specifically, the FDA Reviewer wrote:

Pharmacology recommends approval of this drug [ezetimibe] for monotherapy for the proposed indication [use], but preclinical studies do not support safety of ezetimibe in combination with statins.

Generally, a NOAEL could not be established. The toxicity profile appears to be that associated with statins. . . .

However the toxicity appears at lower duration and exposure than in statin monotherapy.

She further noted that toxicity seen when Zetia was used alone occurred in the heart, lymph nodes, kidneys and bone marrow in laboratory animals; an earlier pharmacology review found lung and liver toxicity as well. When Zetia was combined with a statin, toxicity was seen in even more organs: liver, stomach, skeletal muscle, spleen, heart, lungs, testes, and prostate.

Adverse Reactions Seen in Clinical Trials

Muscle: A major safety concern with cholesterol lowering drugs, particularly the statins, is the possibility of rhabdomyolysis, a breakdown of muscle. This potentially fatal adverse effect led to the withdrawal of cerivastatin in 2001. The FDA Medical Officer conducting the Zetia safety review of clinical trials noted that patients taking Zetia were more likely to have elevations of a blood enzyme known as creatinine phosphokinase (CPK), an early signal of muscle toxicity and a risk

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factor for the possible development of rhabdomyolysis.

In the clinical trials, 2.1 percent of Zetia patients and 1.3 percent of placebo patients had CPK levels greater than three times the upper limit of the normal value. An even greater CPK increase (greater than ten times the upper limit of normal) was seen in 0.2 percent of the patients receiving Zetia and 0.1 percent given the placebo. Moreover, when Zetia was added to a statin, the incidence of muscle pain jumped from 2.6 percent to 4.5 percent.

Liver: There was an elevation of a liver enzyme that was greater than three times the upper limit of normal levels (a warning signal for liver damage) **in 0.0 percent of patients receiving placebo, 0.8 percent of patients taking Zetia alone (10 milligrams per day), 1.0 percent of patients taking a statin alone, and 2.1 percent of patients taking both Zetia (10 milligrams) plus a statin.**

Post-marketing adverse reactions of combination therapy (medical literature)

Two case reports published in the April 20, 2004 *Annals of Internal Medicine* suggest that Zetia may trigger muscle and tendon pain when it is added to statin treatment. Unexpected muscle pain can be another early signal for rhabdomyolysis.

Post-marketing adverse reactions Zetia and combination (FDA reports)

We examined the FDA's adverse drug reaction database from late 2002, when Zetia was approved, through September 2003, to see what kinds of adverse reactions were being voluntarily reported. Since as few as one-in-ten serious adverse drug reactions are reported to the FDA, the numbers of cases we found can probably be multiplied by ten.

Muscle: Twenty cases of rhabdomyolysis were reported in patients taking ezetimibe by itself (without a statin or a fibrate, another class of lipid lowering drugs), one with kidney failure. There was one additional report of rhabdomyolysis when Zetia was used in combination with a statin. Although no patient developed rhabdomyolysis in pre-approval clinical trials, those trials were only 3 months long, and patients were carefully monitored to catch any problems early, before they could develop into anything more serious. In addition to the rhabdomyolysis, we found 83 reports of increased CPK blood levels in patients taking Zetia alone with only two cases of elevations in patients taking the combination Zetia with a statin. Now that Vytorin is approved, the incidence will undoubtedly increase.

Liver: Liver toxicity is also a concern. The statin drugs are known to cause elevations in the blood levels of liver enzymes, an early signal of more serious liver toxicity, and this information is carried in the professional product labeling or package inserts for the statins (see *Worst Pills, Best Pills News* January 2001). We have found that Zetia can also cause elevations of liver enzymes, with 106 cases being reported for patients taking Zetia *without a statin*. There have been two reports of liver failure, one in a patient taking Zetia alone and one in a patient taking both Zetia and a statin.

Zetia's professional product labeling cautions that when the drug is used in combination with a statin, liver function tests should be performed at the initiation of treatment and according to the recommendations for the statin drug being used. Whether those taking Zetia alone also need monitoring is not yet known, but Zetia does appear to have liver toxicity on its own.

Other target organs: FDA has received multiple adverse reaction reports of patients taking Zetia where other organ systems (besides muscle and liver) have been harmed: these included the heart, gastrointestinal tract, and skin. Eleven deaths had also been reported (as of September 30, 2003), 8 of which were related to the heart (chest pain, angina, or heart attack); there was also one death due to liver failure, and one to pancreatitis.

In July and September 2004, FDA added new warnings to the list of adverse events associated with the use of Zetia in the drug's professional product labeling. These warnings followed reports coming into the FDA of hypersensitivity reactions, angioedema, inflammation of the gallbladder, gallstones, pancreatitis and nausea. Angioedema is a serious allergic skin condition characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the heart, liver, or intestine.

Alternate treatments for high cholesterol

It is our view that Zetia and Vytorin (Zetia combined with simvastatin) are not first-choice drugs for treating high cholesterol: they have not been shown to have any health benefits, e.g., to reduce the risk of a first or second heart attack or stroke in people with high cholesterol, as have some of the other cholesterol lowering drugs (the FDA does allow the statin drugs on their own, lovastatin, pravastatin, and simvastatin, to make such claims). We have further concerns about Vytorin, since both animal toxicology studies and clinical trials indicate an increase in adverse effects compared with either drug alone.

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Reporting Rate For Kidney Damage Is 75 Times Higher With Crestor (Rosuvastatin) Than In Patients Taking Other Cholesterol Lowering Statin Drugs.

Public Citizen Renews Call For Crestor To Be Removed From Market

In a letter sent to the Food and Drug Administration (FDA) on October 29, 2004, Public Citizen again urged the immediate withdrawal of the uniquely dangerous cholesterol lowering statin drug Crestor (rosuvastatin) from the market.

The letter was prompted by a new Public Citizen analysis of

adverse drug reaction reports to the FDA. The analysis found that the rate of reports of kidney failure or damage among patients taking Crestor is 75 times higher than in all patients taking all other statin drugs.

The new analysis also found the reporting rate for rhabdomyolysis (severe muscle deterioration) approached that of Baycol (cerivas-

atin), which was taken off the market in August 2001 because of rhabdomyolysis.

Public Citizen originally petitioned the FDA on March 4, 2004 to have Crestor removed from the market.

To read the letter sent to the FDA on October 29, go to www.worstpills.org.

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The FDA recently approved Lipitor's (atorvastatin's) claim that in adults with multiple risk factors for coronary heart disease (such as age 55 years or greater, smoking, high blood pressure, low levels of good cholesterol (HDL), or a family history of early coronary heart disease), but without clinically evident coronary heart disease, atorvastatin can reduce the risk of a

heart attack.

Niacin extended-release tablets are also approved by the FDA to reduce cholesterol and to reduce the risk of recurrent nonfatal heart attack in patients with a history of a previous heart attack and elevated cholesterol levels. This applies only to the brand name product Niaspan.

What You Can Do

There is no medical reason for

you to be taking Zetia alone (ezetimibe) or Vytorin (Zetia in combination with simvastatin) when there are safer and more effective drugs, in terms of reducing cardiovascular events, on the market.

A life style consisting of a healthy diet, adequate rest, exercise, and no smoking is the best prevention of cardiovascular disease.

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Published monthly by Public Citizen's Health
Research Group. ISSN 1080-2479

The Health Research Group was co-founded in 1971 by Ralph Nader and Sidney Wolfe in Washington, D.C., to fight for the public's health, and to give consumers more control over decisions that affect their health.

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Annual subscription price is \$20.00 (12 issues); two year subscription \$36.00. Mail subscriptions and address changes to *Worst Pills, Best Pills News*, Circulation Department, 1600 20th Street NW, Washington, DC 20009.

Our Web site address is <http://www.worstpills.org>.

Worst Pills, Best Pills News is a member of ISDB, a network of independent drug bulletins which aims to promote international exchange of quality information on drugs and therapeutics.

Black Box Warning To Be Required On All Antidepressants Concerning Suicide Risk In Children And Adolescents

Belatedly, the Food and Drug Administration (FDA) announced on October 15, 2004 that it is taking steps to inform parents and physicians about the risks of antidepressants when these drugs are used to treat major depressive disorder in children and adolescents.

This announcement came more than a year after investigators first learned of concerns over the selective serotonin reuptake inhibitor (SSRI) antidepressant Paxil (paroxetine), ten months after British regulators warned physicians not to use the drugs for children, and eight months after an FDA scientist recommended warning the public about the drugs. It also comes 12 years after Public Citizen's Health Research Group asked the FDA to put a similar warning on the first SSRI, Prozac (fluoxetine).

The FDA has directed manufacturers of antidepressant drugs to add black box warnings to the professional product labeling, or package inserts, about the increased risk of suicidal thinking and behavior in children and adolescents being treated with these agents. A black box warning is the strongest type of warning that the FDA can require.

Unfortunately, patients rarely know of the existence of black box warnings unless they ask their pharmacist for the drug's professional product labeling, and research has shown that black box warnings do little to prevent physicians from prescribing drugs inappropriately.

The drugs involved in the new labeling requirements appear at the end of this article.

The FDA's recommended text for the black box warning reads:

Suicidality in Children and Adolescents

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Antidepressant's Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Antidepressant's Name] is not approved for use in pediatric patients except for patients with [Any approved pediatric claims here].

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD,

obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

The second element of the FDA's plan is perhaps the most important. Namely, providing patients and the parents of patients with objective risk information, written in non-technical language, based on a drug's professional product labeling and placing the risk in a meaningful context. These are called Medication Guides, or MedGuides, for short and are given to patients when the prescription is filled. The FDA has the authority to require this type of information for drugs which present unique public health risks. MedGuides should be provided as soon as possible.

The FDA says that it will work with manufacturers to implement "Unit of Use" packaging for all antidepressants as a means of ensuring that patients and parents receive a MedGuide with every prescription or refill. Unit of use packaging is a method of preparing a medication in an original container, sealed and pre-labeled by the manufacturer, and

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Drug Induced Peripheral Neuropathy From The Fluroquinolone Antibiotics

The Food and Drug Administration (FDA) now requires that the professional product labeling, or package inserts, for all fluroquinolone antibiotics must warn about the possibility of peripheral neuropathy (nerve damage).

A list of the fluroquinolone antibiotics currently available in the U.S. appears at the end of this article.

Peripheral neuropathy describes damage to the peripheral nervous system, the communications network that transmits information concerning movement from the brain and spinal cord (the central

WARNING — Increased Risk Of Tendinitis And Tendon Rupture With All Fluoroquinolone Antibiotics

Public Citizen's Health Research Group successfully petitioned the Food and Drug Administration (FDA) to add a warning for doctors to the labeling, or package for all fluoroquinolone antibiotics, about the risk of tendinitis, including the possibility of complete tendon rupture.

This adverse reaction most frequently involves the Achilles tendon, the tendon that runs from the back of the heel to the calf. Rupture of the Achilles tendon may require surgical repair. Tendons in the rotator cuff (the shoulder), the hand, the biceps, and the thumb have also been involved. This reaction appears to be more common in those taking steroid drugs, in older patients, and in kidney transplant recipients but cases have occurred in people without any of these risk factors. The onset of symptoms is sudden and has occurred as soon as 24 hours after starting treatment with a fluoroquinolone. Most people have recovered completely after one to two months.

If you experience unexpected tendon pain while taking a fluoroquinolone antibiotic stop the drug immediately, call your doctor, and rest.

SUICIDE RISK, from page 93

containing sufficient medication for one normal course of therapy.

What You Can Do

If your child is taking one of the drugs listed below to treat major depressive disorder, do not stop the use of these drugs without consulting the prescribing physician.

Anafranil (clomipramine)
Paxil (paroxetine)
Aventyl (nortriptyline)
Pexeva (paroxetine)
Celexa (citalopram)
Prozac (fluoxetine)
Cymbalta (duloxetine)
Remeron (mirtazapine)
Desyrel (trazodone)
Sarafem (fluoxetine)

Effexor (venlafaxine)
Serzone (nefazodone)
Elavil (amitriptyline)
Sinequan (doxepin)
Lexapro (escitalopram)
Surmontil (trimipramine)
Limbitrol (chlordiazepoxide/amitriptyline)
Symbyax (olanzapine/fluoxetine)
Ludiomil (maprotiline)
Tofranil (imipramine HCl)
Luvox (fluvoxamine)
Tofranil-PM (imipramine)
Marplan (isocarboxazid)
Triavil (perphenazine/amitriptyline)
Nardil (phenelzine)
Vivactil (protriptyline)
Norpramin (desipramine)
Wellbutrin (bupropion)
Pamelor (nortriptyline)
Zoloft (sertraline)
Parnate (tranylcypromine)
Zyban (bupropion)

nervous system) to every other part of the body. Peripheral nerves also send sensory information — such as a message that the feet are cold or a finger is burned — back to the brain and spinal cord. Damage to the peripheral nervous system interferes with these vital motor and sensory connections.

The text of the new warning reads:

WARNINGS

Peripheral Neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias (abnormal sensation) and weakness have been reported in patients receiving quinolones, including [name of fluroquinolone antibiotic]. [Name of fluroquinolone antibiotic] should be discontinued if the patient experiences symptoms

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DO NOT USE!

Manufacturer Finally Admits Heart Risks With The Arthritis Drug Bextra (Valdecoxib)

Pfizer, Inc. of New York announced on October 15, 2004 the existence of a second clinical trial in patients undergoing coronary artery bypass graft (CABG) surgery that confirms an association between the use of their top-selling arthritis drug Bextra (valdecoxib) with an increased risk of serious cardiovascular events.

We reported on the first CABG study showing increased cardiovascular risk in the September 2004 *Worst Pills, Best Pills News*. Public access to the Food and Drug

Administration's (FDA) reviews of this study were the result of a lawsuit we filed against the agency in February 2004.

Patients requiring CABG surgery are at a high risk of serious cardiovascular events because they have pre-existing cardiovascular disease. Bextra appears to contribute to heart attacks and strokes in this group of patients. Also, many patients who require drug treatment for their arthritis are older and may have existing or undetected cardiovascular disease that places them at

a higher risk for serious cardiovascular events.

There is simply no reason why Bextra should be prescribed.

What You Can Do

If you are now taking Bextra contact your doctor. There is no medical reason why you should be taking this drug when safer and less expensive products such as Motrin (ibuprofen) or Naprosyn (naproxen) are available to manage arthritis.

FLUROQUINOLONE, from page 94 of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible

condition.

What You Can Do

If you are taking a fluoroquinolone antibiotic and experience pain, burning, tingling, numbness, and weakness or both, or have problems with light touch, pain,

temperature, position sense, vibratory sensation, and or motor strength or both you should stop the medication immediately and contact your physician.

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Cipro (ciprofloxacin)

Factive (gemifloxacin)

Floxin (ofloxacin)

Levaquin (levofloxacin)

Maxaquin (lomefloxacin)

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