

# WORST PILLS



Health Research Group

Visit Health Research Group's website at  
[www.citizen.org/hrgr/](http://www.citizen.org/hrgr/)

# BEST PILLS

N E W S

SIDNEY M. WOLFE, M.D., EDITOR

APRIL 2002 ♦ VOL. 8, NO. 4

## Do Not Use! Nateglinide (STARLIX) – Not a “Star” for the Management of Type-2 Diabetes

The Food and Drug Administration (FDA) approved nateglinide (STARLIX) in December 2000 to lower blood sugar levels in patients with type-2 diabetes, also referred to as adult onset or non-insulin-dependent diabetes mellitus. It is now the 13th drug approved for type-2 diabetes in this country and the second member of a new class of diabetes drugs known as meglitinides. We

listed the first meglitinide, repaglinide (PRANDIN), as a *Do Not Use* drug in the July 1998 issue of *Worst Pills, Best Pills News* because there are equally or more effective and less expensive drugs with better understood safety on the market to lower blood sugar. Nateglinide is produced by Swiss drug giant Novartis.

Both nateglinide and repaglinide work in a manner

similar to the oldest class of diabetes drugs, the sulfonylureas—glipizide (GLUCOTROL) is an example—by stimulating the release of insulin from cells in the pancreas.

The professional product labeling, or “package insert,” for nateglinide suggests that this drug is minimally effective in lowering blood sugar and another measure

*continued on page 26*

### In this Issue

acetaminophen .....	29	CLOZARIL .....	31	heparin .....	28	progesterin .....	28
ACHROMYCIN .....	29	COUMADIN .....	27	hypericum perforatum .....	29	repaglinide .....	25
ALDACTONE .....	28	COZAAR .....	28	ibuprofen .....	28	RIFADIN .....	29
ALEVE .....	28	CYLERT .....	30	INAPSINE .....	30	rifampin .....	29
alprazolam .....	27	DESOGEN .....	29	levomethadyl .....	30	RIMACTANE .....	29
amiloride .....	28	desogestrel .....	29	levonorgestrel .....	29	SOLFOTON .....	29
AMOXIL .....	29	DIABETA .....	26	LIPITOR .....	29	SPES .....	27
ampicillin .....	29	DILANTIN .....	29	losartan .....	28	spironolactone .....	28
angiotensin converting enzyme (ACE) inhibitors ..	28	DIOVAN .....	28	LUMINAL .....	29	St. JOHN'S WORT .....	29
angiotensin receptor blockers .....	28	droperidol .....	30	metformin .....	26	STARLIX .....	25
angiotensin-II receptor antagonists .....	28	DYRENIUM .....	28	MIDAMOR .....	28	sulfonylureas .....	25
antibiotics .....	29	enalapril .....	28	MOTRIN .....	28	SUMYCIN .....	29
anticonvulsants .....	29	estrogen .....	28	naproxyn .....	28	TASMAR .....	30
ascorbic acid .....	29	ethinyl estradiol and desogestrel .....	28	nateglinide .....	25	TEGRETOL .....	29
atorvastatin .....	29	ethinyl estradiol with drospirenone .....	28	nonsteroidal anti-inflammatory drugs (NSAIDs) .....	28	tetracycline .....	29
CAPOTEN .....	28	FULVICIN .....	29	norethindrone .....	29	tolcapone .....	30
captopril .....	28	GLUCOPHAGE .....	26	norgestrel .....	29	triamterene .....	28
carbamazepine .....	29	GLUCOTROL .....	25	ORLAAM .....	30	trovafloxacin .....	30
CELEBREX .....	28	glyburide .....	26	ORTHO-CEPT .....	29	TROVAN .....	30
celecoxib .....	28	GRIFULVIN V .....	29	PC SPES .....	27	TYLENOL .....	29
clozapine .....	31	GRIS-PEG .....	29	pemoline .....	30	valsartan .....	28
		GRISACTIN .....	29	phenobarbital .....	29	VASOTEC .....	28
		griseofulvin .....	29	phenytoin .....	29	vitamin C .....	29
				potassium sparing diuretics .....	28	warfarin .....	27
				PRANDIN .....	25	XANAX .....	27
						YASMIN .....	28

## STARLIX, from page 25

of diabetes control, hemoglobin A1c (HbA1c) blood levels. The FDA approved use for nateglinide in patients whose blood sugar cannot be adequately controlled by diet and exercise and who have not been treated with oral diabetes drugs. Patients whose blood sugar has not been controlled with the older sulfonylurea class of drugs should not be switched to nateglinide, nor should nateglinide be added to their treatment. If the older drugs do not help, neither will nateglinide.

Nateglinide is approved for use in combination with metformin (GLUCOPHAGE), a member of the biguanide class of diabetes drugs. Nateglinide should not be substituted for metformin.

A study described in nateglinide's package insert found a negligible effect on blood sugar and HbA1c levels even at the drug's highest recommended dose. These results were statistically significant in favor of nateglinide, but as is often the case with many new drugs, the clinical effect was insignificant.

In another clinical trial summarized in the package insert, involving patients whose blood sugar was not controlled after treatment with a sulfonylurea, the effect of nateglinide was compared with the sulfonylurea glyburide (DIABETA). Patients taking nateglinide had significant increases in their average blood sugar and HbA1c levels compared to those taking glyburide, thus worsening their diabetes control.

The editors of *The Medical Letter On Drugs and Therapeutics*, a source we often cite because of its reputation for providing independent drug information, reviewed nateglinide in April 2001. Their conclusion was to the point: "Nateglinide is a short-acting hypoglycemic agent that is less

convenient and less effective than sulfonylureas and much more expensive. Its long term safety remains to be established."

The FDA's Division of Metabolic and Endocrine Drug Products, the group that is responsible for approving new diabetes drugs, has taken Congress' mandate of a new mission for the FDA to heart as the drug industry's partner in the development and marketing of new products. This new mission, along with an outmoded drug approval standard written 40 years ago, will continue to enable new drugs to come on the market even though they may be less effective or more dangerous than older ones. Nateglinide is just one more example of this trend.

Novartis is attempting to create a "hook" to sell nateglinide by spinning its less convenient three times a day dosing requirement into a novel advance in the treatment of type-2 diabetes. The spin goes like this: there is a better correlation between the risk of cardiovascular disease from diabetes and blood sugar levels after eating than there is for fasting blood sugar levels (one of the blood tests usually performed to monitor diabetes treatment). It is thus implied that targeting elevated blood sugar levels after eating reduces cardiovascular risk and this can be accomplished by nateglinide because it must be given three times a day.

A physician associated with Novartis played up post-eating blood sugar levels in the November 17, 2001 issue of the medical journal *The Lancet*. She was quickly taken to task in a January 12, 2002 letter to the journal's editor that emphasized that "no ... data yet support post-prandial glycaemia [elevated blood sugar after eating] as a therapeutic target for cardiovascular risk reduction." The letter pointed out that this is a misleading claim made by manufacturers of the meglitinide

diabetes drugs.

We have only a partial answer to a critical question: will the control of blood sugar with these compounds prevent the long term complications of type-2 diabetes? We have the answer for diabetics who can only use insulin (type-1 diabetes or insulin dependent diabetes) from a clinical trial called the Diabetes Control and Complications Trial (DCCT) published in the April 1, 1998 issue of *Annals of Internal Medicine*. This study found that improved blood sugar control in type-1 diabetics using insulin reduces the eye, nervous system, and kidney complications of the disease. However, it is not known if the results of the DCCT trial apply to type-2 diabetes.

The partial answer we have to the above question comes from the United Kingdom Prospective Diabetes Study (UKPDS) that was reviewed in the March 2000 issue of *Worst Pills, Best Pills News*. This study was begun in the late 1970s to examine the effect of drug treatment in reducing the long term complications of type-2 diabetes. The benefits of treatment were found to differ according to the drug and it was found that controlling blood pressure in diabetics with high blood pressure may be a more effective means of preventing complications than strict control of blood sugar.

Nevertheless, nateglinide was too new to be included in the UKPDS study and there is no evidence that it reduces long term complications of diabetes.

## What You Can Do

There is no sound reason that you should be started on nateglinide if you require drug treatment to control type-2 diabetes. Diet and lifestyle modifications remain the cornerstone for management of this condition.

# California Health Authorities Warn Consumers about Prescription Drugs in Herbal Products

**O**n February 7, 2002, California health authorities warned consumers to stop immediately the use of two dietary supplement drug products, PC SPES and SPES, because they contain prescription drugs not listed on their labels that could cause serious health problems. These unregulated drug supplements are produced by BotanicLab of Brea, California.

A laboratory analysis of these products done by the California Department of Health Services' Food and Drug Branch found that PC SPES contains warfarin and SPES contains alprazolam. Warfarin (COUMADIN) is an anticoagulant (blood thinner) that can lead to uncontrolled bleeding if its use is not monitored by a physician. Alprazolam (XANAX) is one of a family of drugs known as benzodiazepines that includes diazepam (VALIUM) as its best-known member. All benzodiazepines cause drowsiness and even short term use can lead to dependence.

According to BotanicLab, "PC" stands for prostate care and "SPES" is the Latin word for hope. Another word for selling hope in the form of a drug of unproven safety or effectiveness is quackery. The drug, sold for "prostate health," is purported to contain chrysanthemum, dyer's woad, licorice, reishi, san-qi ginseng, rambosia, baikal skullcap and saw palmetto. The saw palmetto comes from domestic sources, while the rest are Chinese herbs.

SPES is a bewildering array of 15 herbs. The producer proclaims "SPES helps support the body

after long term weakness. Only herbal extracts which pass our rigid standards are used. SPES does not contain any artificial ingredients." We wonder how the alprazolam got past the "rigid standards."

*You should avoid the use of dietary supplement drugs except for some vitamins and minerals such as calcium.*

Consumers who have SPES and PC SPES capsules should return them to PC SPES Recall Program, 2900-B Saturn Street, Brea CA 92821 (1-800-458-5854) and demand a refund. The California Department of Health Services' Food and Drug Branch, which is continuing to investigate these products, can be reached at 1-800-495-3232 for more information. The U.S. Food and Drug Administration is assisting in the investiga-

tion and monitoring of the recalls throughout the United States.

The Pure Food and Drug Act of 1906 was written, in part, to assure consumers of the identity of the articles they purchased by requiring disclosure on the label of what is in the bottle. Now, 96 years later, American consumers face the same unregulated marketplace for dietary supplement drugs that may contain unknown ingredients because of the passage of the Dietary Supplement Health and Education Act (DSHEA) of 1994 that for all practical purposes deregulated the production and sale of dietary supplements. The responsibility of the present state of affairs can be laid squarely at the feet of Senators Orrin Hatch (R-UT) and Tom Harkin (D-IA), the primary proponents of DSHEA.

Even doctors and pharmacists, as well as the general public, are in the dark about the quality or purity of dietary supplement drugs now flooding the marketplace. Purchasing these products over the Internet or from the local health food store, an independent pharmacy, a national chain, or your own physician is no guarantee that you will be buying what the labels say is in these concoctions.

## **What You Can Do**

You should avoid the use of dietary supplement drugs except for some vitamins and minerals such as calcium. These unregulated drugs carry the possibility of substantial risk without any proof of benefit.

# Do Not Use!

## The New Birth Control Pill Drospirenone With Ethinyl Estradiol (YASMIN)

The combination birth control pill of ethinyl estradiol with drospirenone (YASMIN) was approved by the Food and Drug Administration (FDA) in April 2001. Combination birth control pills contain the hormones estrogen and progestin. These products are referred to as combined hormonal oral contraceptives. In the case of Yasmin, ethinyl estradiol is the estrogen and drospirenone is the progestin. The difference between Yasmin and the other birth control pills on the market is that drospirenone has never before been marketed in the U.S. and is unlike other progestins that have been available here.

Drospirenone is a close chemical cousin of spironolactone (ALDACTONE), a diuretic or water pill that causes the body to retain potassium. Spironolactone is known as a potassium sparing diuretic and a 3-milligram dose of drospirenone, the amount in a daily pill, is equivalent to 25 milligrams of spironolactone. Two facts cause us to list Yasmin as a *Do Not Use* drug: (1) drospirenone causes elevated blood levels of potassium that may cause serious heart and other health problems such as a change in acid balance of the blood and muscle weakness; and (2) there is no evidence that Yasmin is superior in any way to older contraceptive products.

The use of Yasmin is contraindicated (should not be used) in women with the following

conditions:

- \* Kidney problems;
- \* Liver problems;
- \* Adrenal disease;
- \* Disorders that lead to the formation of blood clots;

*There is no evidence that Yasmin is superior in any way to older contraceptive products.*

- \* A past history of blood clots;
- \* Cerebral-vascular or coronary artery disease;
- \* Known or suspected cancer of the breast;
- \* Cancer of the endometrium or other known or suspected estrogen-dependent cancer;
- \* Undiagnosed abnormal genital bleeding;
- \* Cholestatic jaundice (yellowing of the skin or eyes) of pregnancy or jaundice with prior pill use;

- \* Liver tumor (benign or malignant) or active liver disease;
- \* Known or suspected pregnancy;
- \* Heavy smoking (more than 15 cigarettes per day); and
- \* Being over age 35.

A number of prescription and nonprescription drugs can contribute to increased blood levels of potassium. These include:

- \* Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (MOTRIN), naproxyn (ALEVE), and celecoxib (CELEBREX) when taken long term and daily for the treatment of arthritis and other problems;
- \* Potassium sparing diuretics such as spironolactone, triamterene (DYRENIUM), and amiloride (MIDAMOR);
- \* Potassium supplementation that includes the use of unregulated dietary supplements labeled as containing potassium;
- \* Angiotensin converting enzyme (ACE) inhibitors such as captopril (CAPOTEN) and enalapril (VASOTEC);
- \* Angiotensin receptor blockers, also known as angiotensin-II receptor antagonists, such as losartan (COZAAR) and valsartan (DIOVAN);
- \* Heparin, which is an injectable anticoagulant (blood thinner) that is rarely used outside of the hospital.

The professional product labeling, or "package insert," for

Yasmin specifies that a blood test be done during the first month of use, in order to check potassium level if any of the above listed drugs are also being taken. This blood test is not required for any other birth control pill currently on the market.

Yasmin is required to contain the following bold-faced warning:

**Yasmin contains 3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia [elevated blood levels of potassium] in high-risk patients, comparable to a 25 mg dose of spironolactone. Yasmin should not be used in patients with conditions that predispose to hyperkalemia (i.e. renal insufficiency, hepatic dysfunction and adrenal insufficiency). Women receiving daily, long term treatment for chronic conditions or diseases with medications that may increase serum potassium, should have their serum potassium level checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDs.**

Yasmin and other birth control pills may interact with the following drugs:

\* Rifampin (RIMACTANE, RIFADIN), a drug used for tuberculosis. The breakdown (metabolism) of ethinyl estradiol and some progestins is increased by rifampin. A reduction in

contraceptive effectiveness and an increase in menstrual irregularities have been associated with concomitant use of rifampin.

\* Anticonvulsants such as phenobarbital (LUMINAL, SOLFOTON), phenytoin (DILANTIN), and carbamazepine (TEGRETOL) have been shown to increase the metabolism of ethinyl estradiol and/or some progestins, which could result in a reduction of contraceptive effectiveness.

*Women that use these pills have a doubling in their risk of developing blood clots.*

\* Antibiotics. Pregnancy while taking birth control pills has been reported when oral contraceptives were taken with antibiotics such as ampicillin (AMOXIL), tetracycline (ACHROMYCIN, SUMYCIN), and griseofulvin (FULVICIN, GRIFULVIN V, GRISACTIN, GRIS-PEG).

\* Atorvastatin (LIPITOR), a cholesterol lowering "statin" drug. Coadministration of atorvastatin and an oral

contraceptive increased the absorption of the progestin norethindrone and ethinyl estradiol by approximately 30 percent and 20 percent, respectively.

\* ST. JOHN'S WORT. Herbal supplement preparations containing St. John's Wort (*hypericum perforatum*) may induce liver enzymes that may reduce the effectiveness of oral contraceptives and emergency contraceptive pills. This may also result in breakthrough bleeding.

\* Other. Ascorbic acid (vitamin C) and acetaminophen (TYLENOL) may increase plasma levels of some synthetic estrogens, possibly by inhibition of their metabolism.

In the May 1999 issue of *Worst Pills, Best Pills* we listed another type of combined birth control pill as *Do Not Use*. These are products containing ethinyl estradiol and the progestin desogestrel (DESOGEN, ORTHO-CEPT). Birth control pills containing desogestrel are referred to as third generation oral contraceptives and women that use these pills have a doubling in their risk of developing blood clots compared to second generation oral contraceptives. The second generation oral contraceptives contain the progestins norgestrel, levonorgestrel or norethindrone.

### **What You Can Do**

There is no medical reason that you should be using Yasmin rather than one of the older pills containing the progestins norgestrel, levonorgestrel or norethindrone.

# FDA Strengthens Warnings for Droperidol (INAPSINE) after the Drug Was Banned in Britain

In December 2001 the Food and Drug Administration (FDA) strengthened the warnings and precautions sections of the professional product labeling, or “package insert,” for droperidol (INAPSINE), an injectable tranquilizer frequently used as premedication for anesthesia, as treatment for nausea after anesthesia, and for sedation of agitated patients. Droperidol alters the heart’s electrical conductivity, known as QT prolongation, which has led to a type of fatal heart rhythm disturbances known as *torsades de pointes*.

Specific changes to droperidol’s labeling include a “black box” warning, the most serious warning that the FDA can require. The text of the new warning appears at the end of this article.

Unfortunately, American patients

have been left to face the risk of a fatal heart rhythm disturbance from droperidol while British patients have been spared this possibility. In March 2001, eight months before the FDA announced the new warning for droperidol, British drug regulatory authorities banned the drug from the market. Droperidol joins a growing list of drugs that have been banned in foreign countries for safety reasons but remain available in the U.S. These include: levomethadyl (ORLAAM), used to manage narcotic addiction; pemoline (CYLERT), a drug used for hyperactivity in children; the fluoroquinolone antibiotic trovafloxacin (TROVAN); and the Parkinson’s disease drug tolcapone (TASMAR).

A more business-friendly FDA materialized after Congress passed legislation allowing industry to directly fund the drug approval

process, thus improving the economic performance of the drug companies. This law and the new FDA attitude it has engendered apparently created an additional adverse effect for the public. Rather than banning redundant, dangerous drugs such as droperidol and the others listed above, as other countries have done, the FDA asks for label changes and leaves the drugs on the market. This may be good for a company’s financial health, but poor for the public’s health.

## What You Can Do

Before you or a family member give informed consent prior to a surgical procedure, ask your doctor and the anesthesiologist about using a less dangerous alternative to droperidol.

## WARNING

Cases of QT prolongation and/or *torsades de pointes* have been reported in patients receiving INAPSINE at doses at or below recommended doses. Some cases have occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.

Due to its potential for serious proarrhythmic effects and death, INAPSINE should be reserved for use in the treatment of patients who fail to show an acceptable response to other adequate treatments, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs.

Cases of QT prolongation and serious arrhythmias (e.g., *torsades de pointes*) have been reported in

patients treated with INAPSINE. Based on these reports, all patients should undergo a 12-lead ECG prior to administration of INAPSINE to determine if a prolonged QT interval (i.e., QTc greater than 440 msec for males or 450 msec for females) is present. If there is a prolonged QT interval, INAPSINE should NOT be administered. For patients in whom the potential benefit of INAPSINE treatment is felt to outweigh the risks of potentially serious arrhythmias, ECG monitoring should be performed prior to treatment and continued for 2-3 hours after completing treatment to monitor for arrhythmias.

INAPSINE is contraindicated in patients with known or suspected QT prolongation, including patients

with congenital long QT syndrome.

INAPSINE should be administered with extreme caution to patients who may be at risk for development of prolonged QT syndrome (e.g., congestive heart failure, bradycardia, use of a diuretic, cardiac hypertrophy, hypokalemia, hypomagnesemia, or administration of other drugs known to increase the QT interval). Other risk factors may include age over 65 years, alcohol abuse, and use of agents such as benzodiazepines, volatile anesthetics, and IV opiates. Droperidol should be initiated at a low dose and adjusted upward, with caution, as needed to achieve the desired effect.

# New Safety Labeling Change

## Black Box Warning about Heart Inflammation (Myocarditis) with Clozapine (CLOZARIL)

The black box warning in the professional product labeling or “package insert” for the atypical antipsychotic drug clozapine (CLOZARIL) has been expanded to warn about an increased risk of fatal heart inflammation (myocarditis). A black box warning is the strongest type of warning that the Food and Drug Administration (FDA) can require in a drug’s labeling.

The previously existing boxed warning has been prominently relocated to the beginning of the package insert. A subsection has also been added to the WARNINGS section entitled “Myocarditis” to provide information and guidelines related to this issue.

The new risk information added to the black box follows:

3. MYOCARDITIS  
ANALYSES OF  
POSTMARKETING SAFETY  
DATABASES SUGGEST  
THAT CLOZAPINE IS  
ASSOCIATED WITH AN  
INCREASED RISK OF FATAL  
MYOCARDITIS, ESPE-  
CIALLY DURING, BUT NOT  
LIMITED TO, THE FIRST  
MONTH OF THERAPY. IN  
PATIENTS IN WHOM MYO-  
CARDITIS IS SUSPECTED,  
CLOZAPINE TREATMENT  
SHOULD BE PROMPTLY  
DISCONTINUED.

The new information added to clozapine’s WARNING section appears on page 32. In the WARNINGS section reference is made to numbers of patient years. This is a term used by epidemiologists to reflect the exposure of patients to drugs and can be thought of this way: one patient year equals one patient taking clozapine for one year.

### What You Can Do

You should consider the risk of myocarditis as part of an informed decision to consent to treatment with clozapine for you or a family member. If you are already using clozapine and developed symptoms such as shortness of breath during the night, edema, or heart palpitations after you started using the drug, report this to your doctor.

**Editor:** Sidney M. Wolfe, M.D.  
**Managing Editor:** Phyllis McCarthy  
**Staff Researcher:** Larry D. Sasich, Pharm.D.  
**Information Specialist:** John Paul Fawcett  
**Contributing Editor:** William Hines  
**Proofreader:** Benita Marcus Adler  
**Graphic Production:** Neal Brown  
**President:** Joan Claybrook  
**Founder:** Ralph Nader

**WORST PILLS**   
**BEST PILLS**  
N E W S

© Public Citizen/Health Research Group 2002  
All rights reserved.  
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.

Material in the *Worst Pills, Best Pills News* may not be reprinted without permission from the Editor. Send letters and requests to *Worst Pills, Best Pills News* Editor, 1600 20th Street NW, Washington, DC 20009.

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 website address is <http://www.citizen.org/hrg>

*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.

## WARNINGS

### Myocarditis

Post-marketing surveillance data from four countries that employ hematological [blood] monitoring of clozapine treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients (August 2001); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (April 2001); 30 reports of myocarditis with 8 fatalities in 24,108 U.K. patients (August 2001); 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999). These reports represent an incidence of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient years, respectively. The number of fatalities represent an incidence of 2.8, 2.3, 11.5, and 32.2 cases/100,000 patient years, respectively.

The overall incidence rate of myocarditis in patients with schizophrenia treated with antipsychotic agents is unknown. However, for the established market economies (WHO), the incidence of myocarditis is 0.3 cases/100,000 patient years and the fatality rate is 0.2 cases/

100,000 patient years. Therefore, the rate of myocarditis in clozapine treated patients appears to be 17-322 times greater than the general population and is associated with an increased risk of fatal myocarditis that is 14-161 times greater than the general population.

The total reports of myocarditis for these four countries was 82 of which 51 (62 percent) occurred within the first month of clozapine treatment, 25 (30 percent) occurred after the first month of therapy and 6 (7 percent) were unknown. The median duration of treatment was 3 weeks. Of 5 patients rechallenged with clozapine, 3 had a recurrence of myocarditis. Of the 82 reports, 31 (38 percent) were fatal and the 25 patients who died had evidence of myocarditis at autopsy. These data also suggest that the incidence of fatal myocarditis may be highest during the first month of therapy.

Therefore, the possibility of myocarditis should be consid-

ered in patients receiving Clozaril (clozapine) who present with unexplained fatigue, dyspnea [difficult breathing], tachypnea [fast breathing], fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic [EKG or ECG] findings such as ST-T wave abnormalities or arrhythmias. It is not known whether eosinophilia [an increase in the number of certain white cells] is a reliable predictor of myocarditis. Tachycardia [rapid heart rate], which has been associated with Clozaril (Clozapine) treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis.

Prompt discontinuation of Clozaril (clozapine) treatment is warranted upon suspicion of myocarditis. Patients with clozapine related myocarditis should not be rechallenged [restarted] with Clozaril (clozapine).

### Worst Pills, Best Pills News Reply Form

Name (Mr. / Ms.) \_\_\_\_\_

Address \_\_\_\_\_

City / State / Zip \_\_\_\_\_

PNAAA5

**Yearly subscription rate \$20;**  
**two-year subscription rate \$36.00.**  
**Please clip this form and mail it to: Public Citizen; 1600**  
**20th Street, NW; Washington, DC 20009.** Enclose  
your check or money order made  
out to *Pills News*.

**Moving???** Don't forget to take us with you. Return your  
mailing label with your new address.

**Duplicate Mailing???** If you are receiving duplicate copies  
of our publications send us both mailing labels with the  
correct label identified.