

Petition to Add Information About Sildenafil's (Viagra's) Dangers to the Drug Label

July 1, 1998

Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Md. 20857

Dear Dr. Friedman,

The purposes of this letter are to petition FDA to change the labeling and other sources of information about Viagra to add important information about the drug's dangers currently missing from such sources and to warn doctors and patients that a substantial proportion of patients using the drug are unwittingly using it to treat impotence or other types of sexual dysfunction which are probably adverse reactions caused or worsened by other drugs known to impair sexual function.

Most of the information and data upon which the first part of this petition is based, concerning Viagra's safety, is taken from the documents comprising the FDA's own review of sildenafil, conducted before the drug was cleared for marketing.

There are several extremely troubling safety problems in the FDA's review of sildenafil. Most of these are not included in the FDA-approved labeling for Viagra, the unregulated patient information leaflets given to patients when they get their prescription filled, FDA's "Consumer Information about Viagra" (FDA web site, 4/30/98) or in the "Dear Doctor" letter sent by Pfizer to doctors in May, 1998.

Men With Diseases Which Would Have Excluded Them from Pre-Approval Experiments but Who are not Excluded from Viagra Use Now

In all of the large multi-center clinical trials of Viagra, men with various medical conditions were excluded from the studies. Among those excluded were people with blood pressures of less than 90/50 or more than 170/100; active peptic ulcer disease or bleeding disorder; any clinically significant baseline laboratory abnormality, need for anticoagulants, androgens, or trazodone (an antidepressant); need for aspirin or NSAIDs and a history of peptic ulcer disease; history of retinitis pigmentosa; uncontrolled diabetes or diabetic retinopathy; stroke or myocardial infarction within 6 months, cardiac failure, unstable angina, ECG ischemia (a common finding in people with coronary artery disease); or life-threatening arrhythmia within 6 months. **For none of these conditions is there an exclusion in the FDA-approved labeling for sildenafil.**

Thus, people whom investigators correctly thought might be at higher risk for adverse effects of sildenafil were usually excluded from the pre-approval experiments using the drug but people with such diseases are not excluded from using the drug now that it is on the market. The risks of this double standard are self-evident. It is especially irresponsible for Pfizer and others to ascribe deaths from cardiovascular events in people using Viagra to the fact that the patients were at increased risk of cardiovascular disease (such as the following exclusions listed above: blood pressures of less than 90/50 or more than 170/100; uncontrolled diabetes or diabetic retinopathy; stroke or myocardial infarction within 6 months, cardiac failure, unstable angina, ECG ischemia (electrocardiographic evidence of inadequate blood supply to the heart); or life-threatening arrhythmia within 6 months) and therefore that the deaths are not drug-related when many men with these very increased risks were excluded from the pre-approval trials.

If these exclusions were applied to men currently using the drug, the number of people using the drug would be much lower and the overall dangers of the drug would be lessened. Because people with such medical problems were excluded from the controlled trials of Viagra based on the possibility that they would be at increased risk of adverse effects, only now, with the mass marketing to hundreds of thousands of men, many with these medical problems, is the "experiment" to find out about their increased risk being performed.

Significant Lowering of Blood Pressure by Viagra Alone and with Drugs other Than Nitrates

In laboratory studies involving animals, sildenafil caused a drop in blood pressure in 40 percent of the animals and increased the heart rate in 18 percent of the animals. Significant blood pressure lowering effects were also seen in human studies. As mentioned above, men with blood pressure less than 90/50 were excluded from some of the studies and in people with these low blood pressures, now not

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More information on sildenafil (Viagra)

- [Petition to Require a Black Box Warning for Erectile Dysfunction Drugs Sildenafil \(Viagra\), Tadalafil \(Cialis\) and Vardenafil \(Levitra\) to Warn of the Potential for Irreversible Vision Loss](#), October 20, 2005
- [Letter Urging the Therapeutic Products Program in Canada to Require Warnings on the Label of Sildenafil \(Viagra\)](#), August 24, 1998
- [Letter Urging FDA to Convene an Advisory Committee to Review Problems Related to the Use of Sildenafil \(Viagra\)](#), August 20, 1998
- [Letter Requesting Warnings on Sildenafil \(Viagra\)](#), August 27, 1998
- [Petition to Add Information about Sildenafil's \(Viagra's\) Dangers to the Drug's Label](#), July 1, 1998

own, there was also a significant further lowering of blood pressure by Viagra in one study in people already stabilized on amlodipine (Norvasc), a calcium channel blocking drug used for the treatment of hypertension. Subjects on a stable dose of amlodipine were given a single oral 100 mg dose of sildenafil after an overnight fast. "By the sponsor's analyses, most of the treatment group differences were nominally highly statistically significant" [referring to additional decreases in systolic and diastolic pressure, both supine and standing.] Blood pressure effects occurred between an hour to several hours after the dose. "Although substantial, subjects were not symptomatic, at least under the controlled clinical conditions."

The drug's effect on blood pressure has previously been addressed as a major safety concern, and men who are taking drugs like nitroglycerin (called nitrates) to control chest pain (angina) should not take sildenafil because the nitrates also affect blood pressure. Shortly after the drug was approved, six additional deaths were reported to the drug's maker, Pfizer Inc. of New York, and Pfizer sent out a "Dear Doctor" letter to remind physicians that sildenafil must not be used by men who are taking nitrates to control chest pain. (A list of nitrate drugs follows)

Effects on Vision: Understated in Labeling and Other Information

Vision abnormalities are another troubling adverse effect of sildenafil. The professional product labeling, or package insert, for the drug states that abnormal vision, usually a color tinge but also increased sensitivity to light or blurred vision, were seen in some studies in as many as 11 percent of men using the drug. Sildenafil works by inhibiting an enzyme, phosphodiesterase, a form of which is found in many parts of the body including the eye. Some scientists think changes in this enzyme can lead to some types of a serious disorder called retinitis pigmentosa, which in turn can cause retinal degeneration and loss of vision.

In a single dose study (doses of 100-800 mg), visual disturbances were seen in about half the subjects at doses >100 mg and included difficulty seeing in dim light, color aberration, and color tinges. The duration of these events increased with dose. "Effects attributable to inhibition of retinal phosphodiesterase appeared at doses >100 mg."

Another study in healthy male volunteers found dose-related color discrimination errors beginning at 100mg which lasted a few hours.

A third study looked at visual function in 8 normal males and 8 subjects with diabetic retinopathy, given either 200 mg drug or placebo in a crossover design: the photopic electroretinogram (ERG) showed a 50% reduction in amplitude in the response to blue light at both 1.25 and 5 hours postdose (aberration in color vision was actually seen with most colors). There were delays in the ERG waveform in both the light- and dark-adapted states in normals; none of the diabetics underwent the ERG test.

It should be noted that although the most serious and common visual abnormalities occurred at doses greater than the recommended maximum dose of 100 mg per day, the most common violation of the protocol in the studies on the drug was taking more than one dose a day. In addition, a 125 pound man taking 100 mg would be getting twice the dose per pound as a 250 pound man taking the same dose. In the unregulated patient information leaflets currently being dispensed with Viagra, it states "Take only as directed, **usually** once daily as needed." (emphasis supplied). Thus the directions for patients do not clearly warn against taking more than 100 mg a day, assuming this leaflet accompanies a prescription for the 100 mg dosage form.

Drugs Which Can Cause Sexual Dysfunction Including Impotence

Sexual dysfunction consists of a variety of complaints which include (either alone or in combination) loss of desire, inability to initiate or maintain an erection, ejaculatory failure, premature ejaculation, or inability to achieve orgasm. Impotence is simply defined as the failure to achieve erection, ejaculation, or both. A number of diseases can potentially cause sexual dysfunction, as can a large number of drugs. (A list of these medications is printed below.) There is a serious question as to whether patients, were they adequately informed, would choose to use sildenafil to treat the sexual adverse effects of another drug, especially if an alternative drug which did not cause sexual dysfunction or a lower dose of the same drug or would obviate the need for sildenafil.

Many commonly used drugs can interfere with sexual function in both men and women, causing loss of libido, or can interfere with erection or ejaculation in men, or can delay or prevent orgasm in women. Drug-related effects on sexual function may be difficult to distinguish from the effects of depression or disease, but most are reversible when drug use is stopped and sometimes when dosage is decreased.

This list of drugs was originally prepared by the editors of *The Medical Letter on Drugs and Therapeutics*, a highly respected independent source of drug information, written for doctors and

In the first 174 adverse reaction reports received by FDA since Viagra was marketed and up to June 30, 1998, 75 listed one or more drugs being taken by the patient in addition to Viagra. Of these 75 reports, the other drugs were fully listed in 69 of the reports. Of these 69 adverse reaction reports, 32 (46.4%) included one or more drugs known to cause sexual dysfunction.

Of the 75 reports in which patients were using one or more drugs in addition to Viagra, in 27 or 36%, one or more drugs for the treatment of cardiovascular diseases were used, many of which were probably the diseases for which people were excluded in the pre-approval clinical trials.

Some of the cardiovascular disease (including diabetes) for which people are taking these drugs, in addition to Viagra, are themselves associated with an increased amount of sexual dysfunction. But to worsen pre-existing sexual dysfunction and then treat this with Viagra, instead of attempting to substitute another drug less likely to cause sexual dysfunction or to lower the dose of the offending drug seems to be an unwise medical decision, if indeed it is being made with full knowledge.

List of Drugs Which Can Cause Sexual Dysfunction

(Patients should not stop using or modify the dose of any of these drugs without consulting their physicians)

Heart and Blood Vessel Drugs

Antianginal Drugs:

digoxin (Lanoxin); nifedipine (Adalat, Adalat CC, Procardia, Procardia XL); verapamil (Calan, Covera HS, Isoptin, Verelan)

Antiarrhythmics:

amiodarone (Cordarone); disopyramide (Norpace); mexiletine (Mexitil)

Blood Vessel Dilators:

papaverine (Cerespan)

Cholesterol-lowering Drugs:

clofibrate (Atromid-S); gemfibrozil (Lopid)

High Blood Pressure Drugs, (Beta-blockers):

atenolol (Tenormin); betaxolol (Kerlone); bisoprolol (ZeBeta); carteolol (Cartrol); carvedilol (Coreg); labetalol (Normodyne, Trandate); metoprolol (Lopressor); penbutolol (Levato); propranolol (Inderal); timolol (Blocadren)

High Blood Pressure Drugs, (Diuretics):

amiloride (Madamor); chlorthalidone (Hygroton); hydrochlorothiazide (HydroDiuril); indapamide (Lozol)

High Blood Pressure Drugs, (Other):

ALDACTONE; ALDOMET; APRESOLINE; CATAPRES; clonidine (Catapres); guanabenz (Wytensin); guanadrel (Hylorel); guanethidine (Ismelin); guanfacine (Tenex); hydralazine (Apresoline); mecamylamine (Inversene); methyldopa (Aldomet); metyrosine (Demser); prazosin (Minipress); reserpine (Serpasil); spironolactone (Aldactone)

Antibiotics and Other Anti-Infective Agents

ketoconazole (Nizoral)

Anticholinergic Drugs

anisotropine (Valpin); clidinium (Quarzan); dicyclomine (Bentyl); glycopyrrolate (Robinul); homatropine (Isopto Homatropine); isopropamide (Darbid); mepenzolate (Cantil); methanetheline (Banthine); methscopolamine (Pamine); oxybutynin (Ditropan); propantheline (Pro-Banthine); scopolamine (Transderm Scop); tridihexethyl (Pathilon)

Cancer Drugs

interferon alfa (Intron A); leuprolide (Lupron); methotrexate (Rheumatrex); tamoxifen (Nolvadex)

Eye Drugs

acetazolamide (Diamox)

Gastrointestinal Drugs

cimetidine (Tagamet, Tagamet HB); famotidine (Pepcid); metoclopramide (Reglan); nizatidine (Axid); omeprazole (Prilosec); ranitidine (Zantac); sulfasalazine (Azulfidine EN)

amitriptyline (Elavil); amoxapine (Asendin); desipramine (Norpramin); doxepin (Sinequan); fluoxetine (Prozac); fluvoxamine (Luvox); imipramine (Tofranil); isocarboxazid (Marplan); lithium (Lithobid); maprotiline (Ludiomil); nefazodone (Serzone); nortriptyline (Norpramine); paroxetine (Zoloft); PAXIL; PERTOFRANE; phenelzine (Nardil); protriptyline (Vivactil); trancylpromine (Parnate); trazodone (Desyrel); venlafaxine (Effexor)

Antipsychotics:

chlorpromazine (Thorazine); chlorprothixene (Taractan); clozapine (Clozaril); fluphenazine (Prolixin); haloperidol (Haldol); mesoridazine (Serentil); molidone (Moban); olanzapine (Zyprexa); perphenazine (Trilafon); pimozide (Orap); risperidone (Resperdal); thioridazine (Mellaril); thiothixene (Navane); trifluoperazine (Stelazine)

Barbiturates:

pentobarbital (Nembutal)

Tranquilizers:

alprazolam (Xanax); buspirone Buspar); diazepam (Valium)

Neurological Drugs

Anticonvulsants:

carbamazepine (Tegretol) ; ethosuximide (Zarontin); phenytoin (Dilantin)

Antiparkinsonians:

bromocriptine (Parlodel); levodopa (Dopar); pergolide (Permax)

Painkillers/Narcotics

indomethacin (Indocin); methadone (Dolophine); naltrexone (Trexan); naproxen (Naproxyn)

Other Drugs

alcohol; baclofen (Lioresal); cocaine; danazol (Danocrine); diethylpropion (Tenuate); disulfuram (Antabuse); etretinate (Tegison); fat emulsion (Intralipid); finasteride (Proscar); mazindol (Sanorex); nafarelin (Synarel); phenmetrazine (Plegine); phentermine (Ionamin); propofol (Diprivan); testosterone (Depo-Testosterone)

Drugs Containing Nitrates: Do Not Use With Viagra

Nitroglycerin Containing Drugs:

Deponit; Minitran; Nitrek; Nitro-Bid; Nitrocine; Nitro-Derm; Nitro Disc; Nitro-Dur; Nitrogard; Nitroglycerin; Nitroglycerin T/R; Nitroglyn; Nitrol Ointment; Nitrolan; Nitrolingual Spray; Nitrong; Nitropar; Nitropress; Nitroprex; Nitro S.A.; Nitrospan; Nitrostat; Nitro-Trans System; Nitro Transdermal; Nitro-Time; Transderm-Nitro; Tridil.

Isosorbide Mononitrate Containing Drugs:

Imdur; ISMO; Isosorbide Mononitrate; Monoket; Isosorbide Nitrate; Dilatrate-SR; Iso-bid; Isordil; Isordil Tembids; Isosorbide Dinitrate; Isosorbide Dinitrate LA; Sorbitrate; Sorbitrate SA.

Pentaerythritol Tetranitrate Containing Drugs:

Peritrate; Peritrate SA.

Erythryl Tetranitrate Containing Drugs:

Cardilate.

Isosorbide Dinitrate/Phenobarbital Containing Drugs:

Isordil w/PB.

Illicit Substances Containing Nitrates:

Amyl nitrate or nitrite that goes by various names, including "poppers" and butyl nitrate.

Summary

We urge you to act immediately to protect American patients by changing the labeling for Viagra to include more information about adverse effects on vision, dangers of use with certain drugs for treating hypertension and to contraindicate the drug in people with the diseases or conditions which served as a basis for exclusion during the clinical trials. In addition, doctors and patients need to be informed about the long list of drugs which can cause impotence or other forms of sexual dysfunction in order to decrease the likelihood that Viagra is being used as a treatment for drug-induced sexual dysfunction.

Sidney M. Wolfe, M.D.
Director

Larry Sasich, Pharm. D., M.P.H.

Elizabeth Barbehenn, Ph.D.
Staff Pharmacologist