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Irritable Bowel Syndrome (IBS) Drug Alosetron (LOTRONEX) Withdrawn From the Market

Glaxo Wellcome, the producer of the dangerous irritable bowel syndrome (IBS) drug alosetron (LOTRONEX), announced on November 28, 2000 that, at the request of the Food and Drug Administration (FDA), the drug would be withdrawn from the market. Alosetron caused numerous cases of ischemic colitis, a decrease of blood flow to the GI tract that can lead to inflammation, bleeding, and perforation of the GI tract resulting in infection of the abdominal cavity. Severe constipation was an adverse reaction also seen with alosetron.

Ischemic colitis and severe constipation are not "nuisance" effects that will necessarily go away if the offending drug is stopped. Correction of these adverse reactions may require abdominal surgery and the risks that accompany it, and can result in death.

Alosetron was approved in February 2000 after inappropriately receiving a priority ("fast track") review by the FDA. The drug was reviewed by the FDA Gastrointestinal Drugs Advisory Committee on November 16, 1999. During this meeting four cases of ischemic colitis that occurred during clinical trials were discussed. Glaxo Wellcome claimed that the cases were not due to the drug, and a majority of the advisory committee voted to recommend its approval for marketing.

The drug was on pharmacy shelves by March 2000 and three months later the FDA called another meeting of the Gastrointestinal Drugs Advisory Committee to discuss safety problems including cases of ischemic colitis and complications of severe constipation. Between February and June, the FDA had received seven postmarketing reports of serious complications of constipation, resulting in hospitalization for six patients, of whom three required surgery. In this same period, the FDA received eight postmarketing reports of ischemic colitis, four of which resulted in hospitalization and the other four in endoscopic procedures.

The FDA's response to these

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mounting reports of toxicity was predictable: The agency strengthened warnings on the drug's labeling, a strategy that has frequently failed to protect patients from adverse reactions. The agency also, for the first time, required pharmacists to distribute FDA-approved risk information with each new and refill prescription for alosetron. This information should be required for all drugs, but in the case of alosetron it appears that written patient information was used as an excuse to keep the drug from being banned.

In the August 2000 issue of *Worst Pills, Best Pills News,* we listed alosetron as a *Do Not Use* drug because of the safety problems that were presented at the June 26 committee meeting. On August 31, Public Citizen's Health Research Group petitioned the FDA to remove it from the market immediately. By this time the FDA was aware of 27 cases of ischemic colitis including those that had occurred during clinical trials. We followed this petition with a letter to FDA Commissioner Jane Henney on October 31, urging again that the drug be withdrawn after we had determined that by October 20 the toll from alosetron had risen to 54 cases of ischemic colitis, including five fatalities.

The FDA continued to receive reports of ischemic colitis and complications of constipation associated with alosetron. Some were reports of death or other serious complications of ischemic colitis that required blood transfusion or surgery. The FDA finally asked Glaxo Wellcome to remove alosetron from the market after an analysis turned up 70 cases of serious reactions to the drug. To place this number in perspective it must be remembered that the FDA estimates that for each report of a serious adverse drug reaction it does receive, 10 go unreported, meaning that instead of a few dozen problem cases, we are talking about several hundred.

Alosetron was a drug that never should have been approved. There was no way to manage the risks that, even before it was marketed, were known to be associated with its use. Which individuals might experience ischemic colitis or severe complications of constipation could not be predicted. Even after the FDA required pharmacists to distribute agency-approved information to patients, including tips on recognizing early symptoms of ischemic colitis and severe constipation, adverse reaction reports continued to mount. Users who did not experience serious problems with this drug got off lucky.

Glaxo Wellcome maintained that those who suffered harm from alosetron did so because doctors prescribed it inappropriately or patients used it incorrectly. They claimed that the problems were not the fault of the drug, and contended that patients suffered because they did not take "personal responsibility" for their own care. This is contemptible victim-blaming.

Questions about alosetron's safety created tension between individual prescribers and patients who believed the drug was a "miracle" on the one hand, and the FDA which has statutory responsibility for the public's health on the other. The FDA has no way of knowing how many IBS patients were helped by the drug, especially because there was a dramatic improvement even in the patients who got a placebo (dummy drug) in pre-marketing studies. There is no system of counting who gets hurt, let alone who is helped after approval, and claims that hundreds of thousands of IBS sufferers received remarkable benefit from alosetron are baseless rhetoric. The most objective evidence about the benefits of alosetron came from clinical trials conducted before the drug was approved. Between 10 percent and 15 percent more women patients responded to alosetron compared to quasi-treatment in the form of a placebo. Response to treatment, either with alosetron or placebo, was a subjective score of improvement in symptoms for two weeks out of four in 12-week clinical trials. This is a very low standard for approving a new drug.

Undoubtedly, some patients benefited when they were taking alosetron, but was it because of this drug? Some patients also responded favorably in clinical trials to the placebo. A new drug intended to treat a condition that waxes and wanes is difficult to evaluate, especially where there is a high response to treatment with placebo. Was the response due to the drug or to a placebo effect? Most of the "miraculous cures" with alosetron may very well have been due to a placebo effect. None were seen in the controlled clinical trials conducted before the drug was approved.

Concern for the public's health intensified as the FDA continued to receive reports of severe reactions associated with the use of alosetron. The FDA's strategy to manage the risks of this drug had failed. They were unmanageable.

The question that the FDA had to answer was: How many lives must be altered, perhaps permanently, or even lost, because of adverse reactions before alosetron would be removed from the market? To appreciate the FDA's position ask yourself the same question.

Alosetron's rapid removal, only nine months after marketing began, should not be viewed as a success of the FDA's postmarketing surveillance system but rather as a failure of its drug approval process.

Alosetron is the sixth new drug approved since mid-1996 that has been removed from the market for safety reasons. In addition, two drugs approved by the FDA in this time period have been banned in other countries but remain on the market here. For all but one of these drugs,

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Do Not Use Before April 2005

Rivastigmine (EXELON)—A Third Drug For Alzheimer's Disease

The Food and Drug Administration (FDA) approved a third drug, rivastigmine (EXELON), in April 2000 for the treatment of mild to moderate dementia of the Alzheimer's type. Rivastigmine was preceded by tacrine (COGNEX) approved in September 1993 and donepezil (ARICEPT) cleared by the FDA in November 1996. Rivastigmine is produced by Novartis Pharmaceuticals of East Hanover, New Jersey.

The editors of *The Medical Letter on Drugs and Therapeutics*, an independent source of drug information written for physicians and pharmacists, concluded their October 2, 2000 review of this newest drug by saying, "…there is no convincing evidence that rivastigmine markedly improves quality of life in patients with Alzheimer's disease or substantially alters progression of the disease." *The Medical Letter* editors had already concluded in earlier reviews of tacrine and donepezil that there is no evidence that either leads to substantial functional improvement or prevents progression of Alzheimer's (see the August 1997 issue of *Worst Pills, Best Pills News*). We agree with *The Medical Letter* editors' opinions on all three of these drugs.

Tacrine sales slumped to the point where the drug's manufacturer, then Warner-Lambert (now merged with Pfizer), announced that effective June 12, 1997 it suspended advertising to physicians and discontinued patient support programs. The drug is still available, however. Tacrine is associated with liver toxicity.

In the September 1999 issue of *Worst Pills, Best Pills News* we reported that the British equivalent of the FDA had required new safety warnings on donepezil's labeling. The U.S. labeling was changed on February 28, 2000 with the addition of the following warnings:

> *Voluntary reports of adverse events temporally associated with Aricept that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block, hemolytic anemia, hyponatremia [low blood sodium levels], pancreatitis [inflammation of the pancreas] and rash.*

All three drugs work by inhibiting an enzyme that breaks down acetylcholine, a brain transmitter, a deficiency of which is thought to play a role in Alzheimer's disease.

The FDA approved rivastigmine on the basis of two clinical trials comparing rivastigmine to an inactive dummy pill (placebo). The effect of the drug was measured using two different rating scales. The first was the Alzheimer's Disease Assessment Scale (ADAS-cog). The ADAS-cog examines selected aspects of a patient's cognitive performance including memory, orientation, attention, reasoning, language and habits. Scores range from 0 to 70, higher scores indicating greater cognitive impairment.

The second rating scale used was the Clinician Interview Based Impression of Change (CIBIC) scale, which uses information from both the patient and physician and is a broad assessment of behavior, general pathology, cognition, and activities of daily living. CIBIC scores range from 1 to 7 with scores of 1, 2, or 3 equaling marked, moderate, or minimal improvement, respectively. A score of 4 is no improvement and scores of 5, 6, or 7 mean minimal, moderate, or marked deterioration,

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serious safety problems were known before their approval.

New drugs are potentially the most dangerous on the market because of how little is known about their safety at the time they are cleared for marketing. On average only about 3,000 patients receive a new drug under carefully controlled conditions for a limited length of time before it is approved. After approval, however, the drug may be prescribed for a lifetime of use by millions of patients with other diseases taking many other drugs. Drugs that are withdrawn from the market or require extensive new safety warnings usually do so within the first five years after approval. That is the reason for our "five-year rule," which is explained immediately below.

What You Can Do

You should not use a new drug until it has been on the market for at least five years unless it is one of those rare "breakthrough" drugs that offers a documented benefit over older treatments about whose safety much more is known.

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in that order.

One of these trials was published in the March 6, 1999 issue of the *British Medical Journal*. It involved 725 patients in Europe and North America and lasted 26 weeks. The patients were randomized to receive daily low dose (1 to 4 milligrams) or high dose treatments (6 to 12 milligrams) with either rivastigmine or placebo.

On the ADAS-cog rating scale, using scores from all the patients who started the study and receiving high dose treatment, the difference from the start of the study between those taking rivastigmine and the placebo was only 1.6 on the 70 point scale. This difference was not reported as statistically significant. However, using less rigorous analyses of the data there was a statistical difference between the treatments on the ADAS-cog rating scale.

The difference in scores on the CIBIC rating scale between those receiving high dose rivastigmine and placebo was less than half a point (0.47) on the 7 point scale at the end of the 26 week study. This difference was statistically significant.

In patients similar to those enrolled in pre-marketing clinical trials, the known benefits of rivastigmine are: (1) a small positive change in ADAS-cog score after 26 weeks compared to no treatment; and (2) a small positive change in the CIBIC rating score after 26 weeks compared to no treatment. This is the regulatory meaning of the phrase: rivastigmine is an effective treatment for mild to moderate dementia of the Alzheimer's type. In everyday language treatment connotes a cure or remedy. This is very different from the regulatory definition.

In clinical trials conducted before rivastigmine was approved, nausea, vomiting, diarrhea, abdominal pain and loss of appetite were the most common adverse effects. Weight loss occurred in some patients. Approximately 20 percent of patients were unable to tolerate high dose rivastigmine because of adverse reactions. The liver toxicity that is seen with tacrine has not been reported with rivastigmine.

Why are we seeing a tide of minimally effective, perhaps injurious, and wasteful "me too" drugs that only raise the cost of care of Alzheimer's disease with a minimally detectable benefit being approved by the FDA? Part of the reason is the 38-year-old law that the FDA must follow to approve new drugs.

In 1962, the Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act established an effectiveness standard for the approval of new drugs. This was in addition to a 1938 requirement to test new drugs for safety before marketing. The 1962 law did not say that a new drug had to be effective before it was cleared for sale. It said there had to be "substantial evidence" of effectiveness, defined in the law as:

> *"... evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, suggested in the labeling or proposed labeling thereof.*

Notice that this law does not require that a new drug be safer or that there is substantial evidence that it is more effective than drugs already on the market. In fact, using this standard it is possible that a new drug can be approved that is less effective and less safe than drugs already on the market. This is clear from the recent epidemic of newly approved drugs that had to be removed from the market for safety reasons.

Over time the default for substantial evidence has evolved to be a statistical showing that the new drug is more effective than no treatment at all, in the form of a placebo, in two clinical trials. If a company can show that its new drug meets this standard, and has been tested for safety, the FDA must allow the company to market the drug. It is the law.

This 38-year-old standard does not allow for answering the question that is most important for patients and physicians: What drug is the safest and most effective for a given condition? The FDA's hands are tied, they do not have the legal authority to require a comparison between a new drug and older drugs as a condition for approval. Only Congress can raise the bar for drug approval by changing the law and every time Congress has raised the bar over the last century patients have benefited from safer and more effective drugs.

What You Can Do

If you are considering rivastigmine treatment for a family member, before starting the drug carefully discuss with your doctor the benefits that can be expected from it. Our well-known "five-year rule" says you should not use a new drug until it has been on the market for at least five years because pre-market testing does not provide a large enough "statistical universe" to make it likely that hidden hazards will show up. The five-year rule clearly seems to apply in the case of rivastigmine.

Older Adults Not Getting the Most Effective Drugs For High Blood Pressure

"You, or at least many of your colleagues, have failed to provide optimal care to your patients with high blood pressure." This stinging critique of physician prescribing practices starts off an editorial in the *Journal of General Internal Medicine* for October 2000 that commented on a Harvard Medical School study of high blood pressure in older adults that appeared in the same issue.

Recommendations from the National Institutes of Health released in 1993 as the fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure ("JNC V" for short) cited thiazide diuretics (water pills) and beta-blockers as the initial treatment for high blood pressure unless specific medical reasons exist for beginning treatment with a different family of drugs. These recommendations came after three major clinical trials in older adults were published in 1991 and 1992, and were confirmed in 1997 with the publication of JNC VI. The 1993 study has been the basis for our recommendations for the initial treatment of high blood pressure in the book *Worst Pills, Best Pills.*

A table of representative brand and generic names of the various families of blood pressure lowering drugs mentioned in the study appears on this page.

Additionally, other controlled clinical trials indicated that patients with certain illnesses were likely to benefit from specific blood pressure drugs. For example, among those with high blood pressure and congestive heart failure or diabetes, an angiotensin converting enzyme (ACE) inhibitor is a good choice based on evidence that ACE inhibitors reduce mortality in patients with congestive heart failure and can reduce kidney damage in diabetic patients. Also, a beta-blocker would be a good choice for most high blood pressure patients with a history of heart attack, because there are also trials showing a reduction in the risk of death when a beta-blocker is used.

The Harvard researchers examined the prescribing practices of physicians for older high blood pressure patients enrolled in the New Jersey Medicaid program from January 1, 1991 through December 31, 1995. This involved 23,748 new users of a high blood pressure drug. Their average age was 76 years and 11,103 had at least one of the following conditions: diabetes, congestive heart failure, history of heart attack, or history of angina (chest pain).

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Nine Families of High Blood Pressure Lowering Drugs with Representative Generic and Brand Names

Alpha Blockers
prazosin (MINIPRESS)
terazosin (HYTRIN)
doxazosin (CARDURA)

Angiotensin Converting Enzyme (ACE) Inhibitors
captopril (CAPOTEN)
enalapril (VASOTEC)
lisinopril (PRINIVIL, ZESTRIL)

Angiotensin Receptor Blockers
losartan (COZAAR)
valsartan (DIOVAN)
candesartan (ATACAND)

Beta-Blockers
atenolol (TENORMIN)
metoprolol (LOPRESSOR, TOPROL XL)
propranolol (INDERAL)

Calcium Channel Blockers
amlodipine (NORVASC)
nifedipine (ADALAT, PROCARDIA)
diltiazem
verapamil

Central Antiadrenergic Agents
methyldopa (ALDOMET)
clonidine (CATAPRESS)

Direct Vasodilators
hydralazine (APRESOLINE)
minoxidil (LONITEN)

Peripheral Antiadrenergic Agents
guanethidine (ISMELIN)
guanadrel (HYLOREL)

Thiazide Diuretics (water pills)
chlorthalidone (HYGROTON, THALITONE)
hydrochlorothiazide (HYDRODIURIL)

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They found that the most commonly prescribed initial blood pressure lowering drugs were calcium channel blockers (42 percent), next were ACE inhibitors (24 percent), followed by thiazides (17 percent), beta-blockers (10 percent), central antiadrenergic agents (4 percent) , peripheral antiadrenergic agents (3 percent), alpha blockers (less than 1 percent), direct vasodilators (less than 1 percent), and angiotensin II receptor blockers (less than 1 percent).

For 12,645 patients with uncomplicated high blood pressure who did not have any of the conditions listed above, calcium channel blockers were the most commonly prescribed initial drugs (38 percent), followed by thiazides (22 percent), ACE inhibitors (21 percent), and beta-blockers (11 percent).

The researchers concluded that despite the results of well done clinical trials and the recommendations contained in JNC V, the prescribing of thiazides and beta-blockers actually declined during the early 1990s. One explanation offered by the researchers has been the effect of aggressive marketing of calcium channel blockers by drug companies for the initial treatment of high blood pressure.

The researchers noted that in addition to issues of quality of care raised by their results, the prescribing practices documented in this study have huge economic implications. The wholesale cost of a one year supply of a calcium channel blocker can be as much as $1,000, compared to less than $15 for hydrochlorothiazide.

There is no reason to believe that the prescribing pattern seen in this study would not also be seen in the prescribing for elderly patients who must pay for their own drugs. It is conceivable that some seniors are having to choose between paying their rent and buying an inappropriate drug for their high blood pressure when the first line drug, hydrochlorothiazide, costs less than two percent of what a calcium channel blocker would cost. If the basis for prescribing high blood pressure drugs were science, more elderly people with high blood pressure would not have to choose between paying their rent and getting the most effective drug treatment.

We strongly support the aggressive-marketing explanation that the researchers suggest. Physicians have allowed big drug companies to advertise their way into the public's medicine cabinet through high powered advertising campaigns. The trend toward prescription drug advertising to the lay public in non-medical journals and on TV, thereby putting patient/consumer pressure on doctors, can only make the situation worse.

What You Can Do

Do Not stop any high blood pressure medication without first consulting your doctor.

If you are being treated for high blood pressure and have never been tried on a low-dose water pill you should ask your doctor: Why not?

Calling all Public Citizen Alumni

We are planning to hold a symposium with an alumni reception as part of our 30th Anniversary celebration.

If you are a former employee, volunteer, intern, or fellow, please contact Public Citizen so that we may provide you with details of the event.

We look forward to hearing from you!

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FDA Safety Office Recommends Warning About Liver Failure With The Cholesterol Lowering "Statin" Drugs

The Food and Drug Administration's (FDA) Office of Postmarketing Drug Risk Assessment (OPDRA) recommended in a memorandum dated May 1, 2000, that liver failure be included as an adverse reaction in the professional product labeling, or "package insert" for the family of cholesterol-lowering drugs known as "statins." The statins now being marketed in the U.S. are atorvastatin (LIPITOR), cerivastatin (BAYCOL), fluvastatin (LESCOL), lovastatin (MEVACOR), pravastatin (PRAVACHOL), and simvastatin (ZOCOR).

The current labeling for these drugs states that elevations in liver function tests, an early indication of possible liver toxicity, have been seen with the use of statins. The labeling also warns that "It is recommended that liver function tests be performed prior to and at 12 weeks following initiation of therapy or the elevation of dose." No mention is presently made of possible liver failure.

An evaluation of reports of potential liver failure was undertaken by OPDRA in response to requests from Merck Research Laboratories and Bristol Myers Squibb to seek over-the-counter status for their statins Zocor and Pravachol, respectively. A total of 90 cases of liver failure had been reported to the FDA for the six statin drugs. Of the 90 cases, 62 were consistent with the agency's definition of liver failure associated with statin use and more than half of these 62 patients died.

The table below lists the number of cases of liver failure reported to the FDA for each of the statins and the date that the drug was approved for use in the U.S. This table cannot be used to estimate a comparative risk of liver failure from the statins because reports of adverse reactions made to the FDA are voluntary and only 1 serious reaction in 10 is reported to the agency. Also, the drugs became available at different times. For example, lovastatin has been on the market the longest and atorvastatin, though only on the market since 1996, is a top seller primarily because of heavy promotion. There were almost 37.7 million prescriptions filled for atorvastatin in 1999, making it the third most frequently prescribed drug in the U.S., while the next closest statin was simvastatin with 19.9 million prescriptions for the year.

Drug	Number of Cases of Liver Failure Reported	Date of FDA Approval
lovastatin	18	1987 August
pravastatin	13	1991 October
atorvastatin	13	1996 December
simvastatin	12	1991 December
fluvastatin	3	1993 December
cerivastatin	3	1997 July

The symptoms of drug-induced liver toxicity are non-specific and may mimic many other illnesses. They include rash, loss of appetite, tiredness, pain on the right side just below the rib cage (where the liver is situated), dark urine or a yellowing of the skin or whites of the eyes (jaundice). The symptoms of liver toxicity may also include fever.

We agree with the OPDRA recommendation to add liver failure to the labeling of the six statin drugs as an adverse reaction. We hope the FDA's upper management heeds the advice.

What You Can Do

You should contact your doctor immediately if you are taking a statin drug and experience the symptoms of liver toxicity listed above.