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Dangerous medications – preventing serious side effects

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Dear Subscriber,

On the following pages you will find four documents:

1) A Patient Handout on the several "dangerous" drugs that have been highlighted in the *Toronto Star* and U.S. news since the FDA official told Congress about them. This Patient Handout covers *Celebrex*, *Crestor* (the statins), and several others.
2) A Patient Handout on JUST the COX-2 inhibitors and naproxen for you to use if patients are asking about only these.
3) A Health Canada Advisory on COX-2 inhibitors.
4) Professional Information for you covering all of these drugs.

You may use your choice of either (or both) of the Patient Handouts to suit your needs. Active subscribers have our permission to reproduce copies of the Patient Handouts for you to hand to your own patients. (Mass reproduction or electronic forwarding or dissemination is not authorized.)

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Patient Handout

"Dangerous Drugs" in the News

The removal from the market of the painkillers *Vioxx* (rofecoxib) and *Bextra* (valdecoxib), because of the possibility that they cause heart attacks and strokes, has led people to question the safety of other medicines. A recent report in the *Toronto Star* newspaper highlighted medicines or medicine groups that the writers felt were unsafe. Additionally, there is some current news about *Celebrex*, which is also a painkiller like *Vioxx* and *Bextra*. You may have heard about these as well. Here is some information to help you understand these medicines.

Cholesterol-lowering medicines-"the statins"

The cholesterol lowering medicines known as "the statins" (examples include *Lipitor*, *Crestor*, *Zocor*, and others) lower levels of bad cholesterol. While they are very effective at lowering cholesterol, they can also rarely cause side effects. Some of the most severe side effects include liver damage and breakdown of muscles which can cause muscle pain and kidney damage. For this reason, your health care professional will order blood tests to check your liver. Also, you should call your health care professional if you start to get muscle pain or weakness, unusual nausea, abdominal pain, fatigue, dark urine, pain when urinating, pale stools, or yellow-looking eyes or skin.

Weight-loss medicines – Meridia (sibutramine) and Xenical (orlistat)

You may have heard about the weight loss medicines called *Meridia* and *Xenical*.

Meridia creates a feeling of fullness, but can also cause high blood pressure and increase the heart rate, which can lead to stroke or heart attack. But those needing to take weight loss products like *Meridia* may already have blood pressure problems. If you take *Meridia*, you should have your blood pressure and heart rate checked regularly. Also, people who have had heart problems or strokes in the past should not use *Meridia*.

Xenical decreases the amount of fat that is absorbed into the body. But that effect can also cause your stool to be oily and loose. Other side effects are stomach cramping, diarrhea, inflammation of the pancreas, and vitamin deficiencies. If you take *Xenical*, you should divide your daily fat intake evenly over your three main meals and take a multivitamin that contains vitamins D, E, K, and beta-carotene. This multivitamin should be taken at least two hours before or after taking your *Xenical*.

Zyban (bupropion)

Zyban is a non-nicotine medicine to help people stop smoking. *Zyban* reduces the nicotine withdrawal symptoms and the urge to smoke. It is more effective when people also go to a patient support program. However, there is concern about a number of side effects. Rarely, patients who are taking *Zyban* have had heart attacks. But, it is hard to tell if they had a heart attack because they have heart disease from years of smoking or if the heart attack happened because of the *Zyban*. Other side effects include thoughts of suicide or suicide attempts and seizures.

If you have had a seizure disorder, eating disorder such as bulimia or anorexia nervosa, or are stopping the use of alcohol or sedatives, you should not take *Zyban* since these conditions may increase the chance of seizures. Also, you should not take more than 150 mg twice a day. With your families help, you should watch for depression or thoughts of suicide or feelings of anxiety, irritability, hostility, severe restlessness, overly excited behavior, or not being able to sleep. These symptoms should be reported to your health care professional immediately. Finally, you

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should check your blood pressure regularly, especially if you are using *Zyban* with a nicotine patch.

The Serotonin Reuptake Inhibitor Antidepressants (SSRIs)

The SSRI antidepressants (such as *Paxil*, *Prozac* and others) are commonly used for anxiety and depression as well as many other conditions. They have been promoted for conditions such as weight loss, incontinence, alcoholism, cocaine dependence, migraines, pain, fibromyalgia, irritable bowel syndrome, compulsive shopping and many other uses. These are considered "off-label" uses or uses for which the medicine has not been officially approved by Health Canada. "Off-label" prescribing is common and can be beneficial for many people. However, recently, concern that use of these antidepressants can lead to an increased risk of aggression, violence, and suicide has surfaced. This is even more concerning because the use of these antidepressants has skyrocketed, particularly for "off-label" uses.

If you or a family member are taking an SSRI antidepressant, you should watch for any of the following symptoms, and if they occur, report them immediately to your health care provider: thoughts of suicide or suicide attempt; new or worsening depression; or anxiety; feeling agitated, irritable or panicky; acting aggressively, violently or in a dangerous manner; being extremely hyperactive in actions and talking; or any other unusual behavior.

Bextra (valdecoxib) and Celebrex (celecoxib)

Bextra and *Celebrex* (celecoxib) are used mainly for arthritis pain, menstrual pain, or other pain. Many experts are concerned that *Bextra* and *Celebrex* can lead to an increased chance of heart problems or stroke. *Bextra* and *Celebrex* are similar to *Vioxx*, which was just taken off the market due to these types of problems. As of April 2005, *Bextra* is no longer available because of these problems as well as the severe rash it can cause. For more information on *Bextra's* withdrawal go to:

http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_17.html.

The chance of a problem in any one patient is very low, but since the problem seems to be related to cardiovascular disease, it makes sense to try to avoid *Celebrex* in patients who have heart problems.

Patients who have heart trouble and are taking *Celebrex* should talk with their health care professional.

People who are not likely to benefit from *Celebrex* may be better off on a regular NSAID (such as *Motrin* or *Advil* or a store's brand product) or acetaminophen (such as *Tylenol* or a store's brand product). Patients should discuss this with their pharmacist and/or physician.

For more information on *Celebrex* go to:
http://www.hc-sc.gc.ca/english/protection/warnings/2004/2004_67_e.html
http://www.pfizer.ca/english/newsroom/press%20releases/default.asp?s=1&releaseID=149

Just recently, the FDA issued a patient advisory statement on naproxen (*Aleve*, *Naprosyn*) which can be bought over-the-counter in the U.S. Preliminary information from an Alzheimer's disease study showed some evidence of increased risk of cardiovascular events in patients taking naproxen. The FDA advises that patients should not exceed the recommended dose of 220 mg twice daily for longer than ten days unless a physician directs otherwise.

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Patient Handout

"Dangerous Drugs" in the News

Remember

Every medicine has side effects. Your pharmacist and/or physician know the possible side effects of drugs and can carefully weigh the benefit of medicines against their risks. Your health care professional will review possible side effects with you and give you information about how to reduce these risks. Be sure to ask any questions you have when a drug is prescribed or dispensed and while you are taking it. Always follow the medication instructions that your health care professional gives you. Never share medications since this is a very dangerous practice. Be sure to get your medicines from a trusted pharmacist.

If you have any concerns, please feel free to discuss them with your health care professional who gave you this handout.

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Information for Patients Taking *Celebrex* or Naproxen

Celebrex (celecoxib) and naproxen are used mainly for pain such as arthritis pain. Many patients also use them for menstrual pain. Many experts are now concerned that *Celebrex* and naproxen can lead to an increased chance of heart problems or stroke. *Celebrex* is similar to *Vioxx* and *Bextra* which were taken off the market due to these types of problems. Naproxen is a regular painkiller like *Motrin* or *Advil.*

The chance of a problem in any one patient is very low. It is important to remember that many millions of people have used these medicines and many are still using them. Researchers continuously conduct studies to learn more about the drugs. Recently, researchers were studying to see if *Celebrex* was useful to prevent colon cancer. During the course of the study researchers noticed that there was an increase in heart problems in the people who were taking *Celebrex.* These studies usually run for years and involve many patients. In this case it requires statistical calculations to determine that there was an increase in heart problems in the patients taking *Celebrex.* Just recently, the FDA issued a patient advisory statement on naproxen (*Aleve, Naprosyn*) which can be bought over-the-counter in the U.S. Preliminary information from an Alzheimer's disease study showed some evidence of increased risk of cardiovascular events in patients taking naproxen. Any individual patient who has taken *Celebrex* or naproxen should not become overly concerned.

Since the problem seems to be related to cardiovascular disease, it makes sense to try to avoid *Celebrex* in patients who have heart problems. Patients who have heart trouble and are taking *Celebrex* or naproxen should talk with their health care professional to see if some other therapy might be better for them.

Bextra, Celebrex, and *Vioxx* are called COX-2 inhibitor drugs. These drugs are actually in the same family of drugs that are called nonsteroidal anti-inflammatory drugs (NSAIDs). One of the problems with some nonsteroidal anti-inflammatory drugs (NSAIDs) is that they can sometimes lead to bleeding in the stomach. It was thought that the COX-2 drugs such as *Bextra, Celebrex,* and *Vioxx* would not lead to as much bleeding in the stomach as the other nonsteroidal anti-inflammatory drugs (NSAIDs). So patients who had ulcers or other chance of bleeding in the stomach or intestinal track often got a drug like *Bextra, Celebrex,* or *Vioxx* instead of the regular nonsteroidal anti-inflammatory drugs (NSAIDs). Pharmaceutical firms encouraged physicians to use these COX-2 drugs for many people. Many people might be better off on a regular NSAID (such as *Motrin, Advil*, or a store's brand product), or acetaminophen (such as *Tylenol* or a store's brand product). Patients should not exceed the recommended dose or duration printed on any over-the-counter medicine bottle unless a physician directs otherwise. Patients should discuss this with their pharmacist and/or physician.

There was a separate concern related to *Bextra*. It could cause severe rash, which in some cases was life-threatening. This reaction was unpredictable, and could happen after short or long periods of use. In April 2005, Health Canada asked Pfizer Canada, the manufacturer of *Bextra*, to voluntarily withdraw *Bextra* from the market.

For more information go to:
http://www.hc-sc.gc.ca/english/protection/warnings/2004/2004_67_e.html
http://www.pfizer.ca/english/newsroom/press%20releases/default.asp?s=1&releaseID=149
http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_17.html

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January 2005 ~ Volume 21 ~ Number 210116

Safety Information Regarding Selective COX-2 Inhibitor NSAIDs: *Vioxx*, (Rofecoxib), *Celebrex* (Celecoxib), *Bextra* (Valdecoxib), *Mobicox* (Meloxicam) and Generic Forms of Meloxicam

The following excerpts are reprinted from the December 22, 2004 Health Canada Advisory on safety information regarding selective COX-2 Inhibitors. http://www.hc-sc.gc.ca/english/protection/warnings/2004/2004_69_e.html

Health Canada wishes to inform Canadians of safety concerns regarding the group of drugs known as selective COX-2 inhibitor NSAIDs (non-steroidal anti-inflammatories). These include *Vioxx* (rofecoxib), which has been withdrawn from the market, *Celebrex* (celecoxib), *Bextra* (valdecoxib), and *Mobicox* (meloxicam), which are used in the treatment of symptoms of rheumatoid arthritis, osteoarthritis and primary dysmenorrhea (menstrual pain).

Accumulating evidence indicates that the use of selective COX-2 inhibitor NSAIDs, in certain individuals, is associated with an increased risk of heart attack or stroke when compared to placebo. The risk appears to increase with the total daily dose and the length of the treatment. However, given the available data, it is not possible to identify which patients would present a higher risk of heart attack and stroke.

Health Canada has requested additional safety information from the manufacturers of *Celebrex*, *Bextra*, *Mobicox* and generic forms of meloxicam, and will continue to review the safety profile of these drugs in order to fully consider what is presently known about the risks and benefits of these drugs when used according to their labelling.

Until further information from long-term clinical trials becomes available, one should consider that there is a strong possibility of an increased risk of cardiovascular events, including heart attack and stroke, when using selective COX-2 inhibitor NSAIDs (*Celebrex*, *Bextra*, *Mobicox*, and all generic forms of meloxicam).

Patients should discuss the benefits and risks of treatment options with their physician, in light of the following information.

Vioxx (rofecoxib)

Vioxx was withdrawn on September 30, 2004, based on new safety information from a three-year, randomized double-blind clinical trial, called APPROVe, showing a possible increased risk of cardiovascular events. The APPROVe (Adenomatous Polyp Prevention on *VIOXX*) clinical trial was designed to assess the effectiveness of 25 mg *Vioxx* in preventing the recurrence of colon polyps (abnormal tissue growth, which may or may not be cancerous). In the APPROVe trial, *Vioxx* was compared to a placebo (sugar pill). Merck & Co withdrew *Vioxx* from the worldwide market after the study indicated an increased risk of serious cardiovascular events, such as heart attacks and strokes, after 18 months of continuous treatment.

Bextra (valdecoxib)

On December 10, 2004, Pfizer Inc. released new information about cardiovascular risks associated with *Bextra*. In a study conducted by Pfizer, which included over 1,500 patients treated for acute pain after coronary artery bypass grafting (CABG), an increased risk of cardiovascular events was observed in patients treated with *Bextra* compared to placebo. These cardiovascular events included myocardial infarction (heart attack), cerebrovascular accident (stroke), deep vein thrombosis (blood clots in the leg), and pulmonary embolism (blood clot in the lung). The risk of these effects was observed to be greater with the intravenous form of the drug

More. . .

(approximately two percent of patients had such an adverse event), in comparison with the oral form of the drug (approximately 1 percent of patients), immediately following CABG surgery. About 0.5 percent of patients taking the placebo had an adverse cardiovascular event.

Celebrex (celecoxib)

On December 17, 2004, the National Cancer Institute (NCI) in the United States announced that it had stopped a three-year *Celebrex* study called Adenoma Prevention with Celecoxib (APC) due to an interim analysis showing a statistically significant increase in the risk of heart attack, stroke and cardiovascular death. Health Canada has withdrawn market authorization for the use of *Celebrex* for the prevention of recurrence of Familial Adenomatous Polyposis, which is predictive of colorectal cancer. *Celebrex* should not be taken for the prevention of recurrence of Familial Adenomatous Polyposis and patients should discuss alternative therapeutic options with their doctors.

Background on Selective COX-2 Inhibitor NSAIDs

Selective COX-2 inhibitor NSAIDs were first authorized for sale in Canada in 1999 based on data showing a better gastrointestinal safety profile than traditional (non-selective) NSAIDs (for example, ibuprofen). There was a need for new therapies because of the well-documented frequent and severe gastrointestinal adverse events (for example ulcers and gastric haemorrhages) associated with the use of traditional (non-selective) NSAIDs. Also, a significant number of patients could not tolerate traditional (non-selective) NSAIDs because of stomach upset.

It should be noted that alternative therapies to selective COX-2 inhibitor NSAIDs also present risks. Therefore, patients should discuss with their physician all benefits and risks of selective COX-2 inhibitor NSAIDs versus alternative therapies, in order to determine the most appropriate treatment in their individual case.

Continue to the next page for more professional information.

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Professional Information

"Dangerous Medications" - Preventing Serious Side Effects

Lead authors: Joseph A. Woelfel, Ph.D., FASCP, R.Ph., Assistant Editor
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Background

The recent removal of the painkiller, *Vioxx* (rofecoxib) because of the possibility that it causes heart attacks and strokes has led people to question the safety of other medicines.[1]

On November 18, 2004, Dr. David Graham testified before the U.S. Senate Committee on Finance. Dr. Graham is the Associate Director for Safety, Office of Drug Safety for the Food and Drug Administration. In his presentation made at the hearing on FDA, "Merck and *Vioxx*: Putting Patient Safety First," he identified five FDA-approved "dangerous drugs." These include the diet drug *Meridia* (sibutramine), the cholesterol drug *Crestor* (rosuvastatin), the acne medication *Accutane* (isotretinoin), the anti-inflammatory drug *Bextra*, and the asthma medicine *Serevent* (salmeterol).[1] The risks associated with these FDA-approved products that Dr. Graham identified are well known. The larger concern is that there may be system problems in checks and balances for rapid drug approval versus safety assurance.

Similarly, a recent report in the *Toronto Star* newspaper highlighted medicines or medicine groups that the writers felt were unsafe.[2-6] The risks associated with these products are well-known and can often be minimized.

Minimizing "Dangerous Drug" Effects

Appropriate prescribing, dispensing, administration, and monitoring of medication use are essential for assurance of patient safety.

The HMG-CoA reductase inhibitors or "statins" such as *Lipitor* (atorvastatin), *Zocor* (simvastatin), or *Crestor* (rosuvastatin) can cause rhabdomyolysis or hepatotoxicity. Patients should report any muscle pain or weakness as well as any signs of liver problems such as yellow skin or sclera. Liver function tests should be routinely monitored and the medication should be stopped if the AST or ALT increases to greater than three times the upper limit of normal.

The consumer advocacy group, Public Citizen, has specifically admonished *Crestor* for causing kidney damage and rhabdomyolysis. In general, the risk of rhabdomyolysis is higher with higher doses. In fact, Health Canada recently released important safety information warning about concerns with the 40 mg dose.[7] The 40 mg dosage must not be used in patients who have pre-existing medical conditions or other factors which put them at increased risk for rhabdomyolysis. This includes Asian ethnicity, serious kidney or liver problems, concomitant use with fibrates or niacin, hypothyroidism, situations where increased *Crestor* blood levels may occur, personal or family history of hereditary muscle problems, previous history of statin-induced muscle toxicity, and alcohol abuse. Patients should be maintained on the lowest dose meeting their therapeutic goal. For Asian patients and all patients with severe renal impairment (CL_{cr} <30 mL/min/1.73m^2), a starting dosage of 5 mg once daily is recommended. The 5 mg dose should be considered for all patients requiring less aggressive LDL-C reductions and those with predisposing factors for myopathy.[7,8]

Meridia (sibutramine) for weight loss can increase blood pressure and also heart rate. Obese patients may already present with underlying heart and vascular problems so caution in prescribing is essential. *Meridia* is under scrutiny from Public Citizen because of these potentially dangerous side effects.[9] Tell patients to check their blood pressure and heart rate regularly, and report any abnormal increases. Emphasize healthy lifestyle changes.[10]

Xenical (orlistat) decreases the amount of fat that is absorbed into the body. But blocking absorption of fat can result in loose, oily stools and diarrhea. Other side effects include stomach

More. . .

cramping, pancreatitis, and vitamin deficiencies. Make sure patients who take *Xenical* divide their daily fat intake evenly over their three main meals and take a multivitamin that contains vitamins D, E, K, and beta-carotene. This multivitamin should be taken at least two hours before or after taking *Xenical*.[11]

Zyban (bupropion) is a non-nicotine medicine approved for smoking cessation. *Zyban* reduces the nicotine withdrawal symptoms and the urge to smoke. It is more effective when patients combine it with a patient support program.

However, there is concern about a number of side effects.[5] Rarely, patients who are taking *Zyban* have had heart attacks. But, smokers are at high risk for cardiovascular disease and it is difficult to establish causality between *Zyban* and the heart attack. Other side effects include thoughts of suicide or suicide attempts and seizures.

Because of the possibility of seizures, patients who have a history of a seizure disorder, an eating disorder such as bulimia or anorexia nervosa, or are discontinuing the use of alcohol or sedatives should not receive *Zyban*, since these conditions may increase the chance of seizures while taking *Zyban*. Also, when used for smoking cessation, the dose should not exceed 150 mg twice a day. As with the serotonin reuptake inhibitor antidepressants, patients and their families should watch for depression; thoughts of suicide; or feelings of anxiety, irritability, hostility, severe restlessness, mania, or insomnia. Finally, blood pressure should be closely monitored, especially if *Zyban* is being used concomitantly with a nicotine patch.[12]

Serotonin reuptake inhibitors (SSRIs) antidepressants [such as *Paxil* (paroxetine), *Prozac* (fluoxetine) and others] are approved for use for anxiety and depression. However, there is a growing list of use in off-label populations such as children and adolescents, and for a variety of off-label uses such as weight loss, incontinence, alcoholism, cocaine dependence, migraines, pain, fibromyalgia, irritable bowel syndrome, compulsive shopping, and many others. With the increasing use in a broader range of patients, concern that use of these antidepressants can lead to an increased risk of aggression, violence, and suicide has surfaced.

Patients, and families of patients taking an SSRI antidepressant, should watch for any of the following symptoms and if they occur, report them immediately: thoughts of suicide or suicide attempt; new or worsening depression or anxiety; agitation or irritability; acting aggressively, violently or in a dangerous manner, mania in actions and talking; or any other unusual behavior.[13]

Bextra (valdecoxib) had new warnings added this December 2004. Serious skin rashes such as toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme can occur anytime but usually occur within the first two weeks of therapy. Advise patients to watch for rashes, lesions, or unusual swelling and discontinue *Bextra* at the first sign of these. They should immediately call their health care professional when this occurs. Additionally, *Bextra* is contraindicated for the treatment of post-coronary bypass surgery (CABG) pain. In this group of patients, *Bextra* is contraindicated due to cardiovascular thromboembolic adverse events. A new bolded warning is being added to the label. Caution should be used when using *Bextra* in patients with ischaemic heart disease or other factors that may predispose to cardiovascular events such as congestive heart failure, unstable angina, uncontrolled hypertension, myocardial infarction, transient ischaemic attacks, and stroke.[14] **On April 7, 2005 Health Canada requested that Pfizer withdraw *Bextra* from the market.[17] For more information on *Bextra's* withdrawal go to: http://www.hc-sc.gc.ca/english/protection/warnings/2005/2005_17.html**.

Celebrex (celecoxib). On December 17, 2004, Pfizer issued a news release that in the Adenoma Prevention with Celecoxib (APC) trial, patients taking 400 mg and 800 mg of *Celebrex* daily had an approximately 2.5 fold increase in major fatal or non-fatal cardiovascular events compared with placebo. As a result of this finding, the APC colon cancer prevention trial was stopped. Though higher-than-recommended doses were used in the trial, these findings further raise safety concerns.[15] For more information go to:
http://www.hcsc.gc.ca/english/protection/warnings/2004/2004_67_e.html
http://www.pfizer.ca/english/newsroom/press%20releases/default.asp?s=1&releaseID=149. On

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April 7, 2005 Health Canada announced new restrictions concerning the use of *Celebrex*.[17] These are:

- Patients who have had a heart attack or stroke, experienced serious chest pain related to heart disease, or who have had serious diseases of the heart such as congestive heart failure, should NOT use this medication
- Patients who have significant risk factors for heart attack or stroke should be aware that using this drug may increase this risk
- This medication should be prescribed and used at the lowest possible dose, and for the shortest, necessary period of time
- Selective COX-2 inhibitor NSAIDs should only be used to treat the pain and inflammation of arthritis, and certain types of acute pain

On December 20, 2004, the FDA issued a patient advisory statement on naproxen (*Aleve*, *Naprosyn*) which can be bought over-the-counter in the U.S. Preliminary information from an Alzheimer's disease study showed some evidence of increased risk of cardiovascular events in patients taking naproxen. The FDA advises that patients should not exceed the recommended dose of 220 mg twice daily for longer than ten days unless a physician directs otherwise.[16]

Active involvement by patients in managing their medication with their health care professionals will minimize the dangerous effects of these drugs.

Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

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