



Health  
Canada

Santé  
Canada

Therapeutic Products Directorate  
Direction des produits thérapeutiques

Therapeutic Products Directorate (TPD) and Biologic and Genetic Therapies Directorate (BGTD) posts safety alerts, public health advisories, press releases and other notices from industry as a service to health professionals, consumers, and other interested parties. Although TPD and BGTD approve therapeutic products, TPD and BGTD do not endorse either the product or the company. Any questions regarding product information should be discussed with your health professional.

This is duplicated text of a letter from **Bristol-Myers Squibb Canada Inc and Linson Pharama Inc.**  
Contact the company for a copy of any references, attachments or enclosures.

## Bristol-Myers Squibb Canada Inc. Linson Pharama Inc.

**IMPORTANT  
SAFETY  
INFORMATION**

June 20, 2001

### **Important Safety Information on NEFAZODONE HCL: Severe and Serious Hepatic Events**

---

Dear Health Care Professional,

Bristol-Myers Squibb Canada Inc. and Linson Pharma Inc. would like to advise you of very rare reports of severe liver injury temporally associated with the use of the antidepressant nefazodone HCl sold by Bristol-Myers Squibb under the tradename Serzone-5HT<sub>2</sub> and by Linson under the tradename LinNefazodone. Nefazodone is indicated for the symptomatic relief of depressive illness.

Nefazodone has been evaluated in more than 8000 clinical trial subjects and has been used by approximately 8.3 million patients worldwide since its market introduction in 1994. **Worldwide post-marketing safety experience has resulted in the identification of 109 serious (requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is life-threatening or results in death) hepatic adverse events in temporal association with nefazodone. These include 23 cases of liver failure worldwide of which 16 led to transplantation and/or death.** Among an estimated 650,000 patients treated with nefazodone in Canada, four cases of liver failure have been reported of which two required liver transplantation. Nefazodone has also been temporally associated with hepatic adverse events such as jaundice, hepatitis and hepatocellular necrosis in patients receiving therapeutic doses. Reporting rates determined on the basis of spontaneously reported post-marketing adverse events are generally presumed to underestimate the risks associated with drug treatments.

Although some of the reported cases of severe hepatic injury have confounding factors such as concomitant medications, alcohol, or the presence of underlying disease, a possible causal role for nefazodone cannot be excluded. Among the cases of liver failure, two-thirds had the onset of symptoms

within the first 4 months of initiation of treatment. Cases of liver injury have occurred as early as a few weeks after initiation of therapy or after continuous use for up to 1-2 years.

Clinical manifestations of severe hepatic injury in patients have included the following: anorexia, fatigue, asthenia, malaise, abdominal pain, nausea, vomiting, discoloured stools, dark urine, prolonged coagulation, weight loss, jaundice, ascites, confusion, asterixis, encephalopathy, and hepatic coma. Laboratory evidence of hepatotoxicity has included increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, (-glutamyl transpeptidase (GGT), and bilirubin, as well as increased prothrombin times.

Prior to prescribing nefazodone, physicians should counsel their patients to be alert to the premonitory signs and symptoms listed above and to seek emergency medical attention if these develop. The appearance of signs and symptoms of hepatotoxicity, or the development of abnormal aminotransferase and/or bilirubin levels while on treatment is an indication for immediate termination of nefazodone treatment and close monitoring of the patient. In most cases, discontinuation of nefazodone has been associated with recovery, while in rare cases hepatic dysfunction has progressed to liver failure and, even less frequently, death, in spite of discontinuation of the drug. The occurrence of liver injury can be fatal even if properly recognized and managed.

Health care professionals are also reminded that nefazodone is a potent inhibitor of the hepatic drug metabolizing enzyme, CYP3A4, and has the potential to decrease the metabolism of many concomitantly administered drugs and other xenobiotics, potentially increasing the toxicity of these agents.

Bristol-Myers Squibb and Linson Pharma continue to work actively with Health Canada to monitor adverse event reports and to ensure that up-to-date information regarding the use of nefazodone is available. Revisions to the existing product monographs with respect to serious liver injury have been requested by Health Canada. Copies of the current product monographs are available on request from Bristol-Myers Squibb (Serzone-5HT2) or Linson (LinNefazodone). Health Care Professionals will be advised of the revisions as soon as possible.

The identification, characterization, and management of drug-related adverse events are dependent on the active participation of healthcare professionals in adverse drug reaction reporting programmes. Any occurrences of hepatic injury or other serious and/or unexpected adverse events should be reported to Bristol-Myers Squibb (Serzone-5HT2) at 1-800-267-1088 Ext. 2293 or by fax at 1-888-267-6211, or to Linson (LinNefazodone) at 1-866-554-6766 or by fax at 1-514-333-4206.

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Yours sincerely,

*original signed by*

---

Vicky Esposito  
Senior Director  
Regulatory Affairs and Quality Assurance  
Bristol-Myers Squibb Canada Inc.

*original signed by*

---

Laura King  
Associate Director  
Regulatory Affairs  
Linson Pharma Inc.

**Any suspected adverse drug reactions can also be reported to:**

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)  
Bureau of Licensed Product Assessment  
Therapeutic Products Directorate  
HEALTH CANADA  
Address Locator: 0201C2  
OTTAWA, Ontario, K1A 1B9  
Tel: (613) 957-0337 or Fax: (613) 957-0335  
[cadrmpp@hc-sc.gc.ca](mailto:cadrmpp@hc-sc.gc.ca)

**The ADR Reporting Form can be found in *The Canadian Compendium of Pharmaceuticals and Specialties*, or on the TPD website, along with the ADR Guidelines at:**

[http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse\\_e.pdf](http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf)  
[http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr\\_guideline\\_e.pdf](http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr_guideline_e.pdf)