Health Canada / Santé Canada

Health Products and Food Branch
Direction générale des produits de santé et des aliments

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This is duplicated text of a letter from **Merck Frosst/Schering Pharmaceuticals**.
Contact the company for a copy of any references, attachments or enclosures.

Health Canada Endorsed Important Safety Information on EZETROL® (ezetimibe)

MERCK FROSST / Schering Pharmaceuticals

February 1, 2005

Subject: Association of Ezetrol® (ezetimibe) with myalgia, rhabdomyolysis, hepatitis, pancreatitis, and thrombocytopenia

Dear Health Care Professional,

Merck Frosst/Schering Pharmaceuticals, following discussions with Health Canada, would like to inform you of new safety data for Ezetrol® (ezetimibe), used alone or in combination with a statin. Ezetimibe is a cholesterol absorption inhibitor that is classified as a systemic drug, because of the enterohepatic recirculation of one of its metabolites[1].

The Product Monograph for Ezetrol® (ezetimibe) has been updated to include information from international post-marketing reports of rare, and in some cases serious, adverse events. The Patient Information section is being updated to inform patients of the signs and symptoms of hepatic, muscle, and pancreatic adverse events, for which early consultation with a physician is recommended.

Additional reports of myalgia, many accompanied by elevated creatine phosphokinase (CK) values, have been reviewed by Health Canada.

The Warnings, Precautions, and Adverse Events sections are being updated to reflect the occurrence of the following adverse events in patients taking Ezetrol® (ezetimibe) alone or in combination with a statin:

- myalgia;
- rhabdomyolysis;
- hepatitis;
- acute pancreatitis;
- thrombocytopenia; and
- suspected interaction between Ezetrol® (ezetimibe) and warfarin

While it is not possible to definitively establish a causal relationship between these adverse events and the use of Ezetrol® (ezetimibe), the Product Monograph changes and the following recommendations are based on the potentially serious nature of these events.

Adverse muscle events:

Myalgia

Myalgia has been reported in patients treated with Ezetrol® (ezetimibe).

Importantly, a number of patients treated with Ezetrol® (ezetimibe) in whom myalgia occurred, had previously experienced myalgia (with or without elevated CK levels) with statin therapy. Patients with a history of statin intolerance (myalgia with or without elevated CK levels) should be closely monitored for adverse muscle events during treatment with Ezetrol® (ezetimibe).

Rhabdomyolysis

Patients treated with Ezetrol® (ezetimibe), who experience persistent muscle pain, should be instructed to contact their physicians for evaluation of the possibility of rhabdomyolysis. In most reported cases, rhabdomyolysis resolved when the drugs were discontinued.

Adverse hepatic events:

Elevations of liver transaminases and cases of hepatitis have been reported in patients treated with Ezetrol® (ezetimibe). Liver function monitoring is recommended when therapy with Ezetrol® (ezetimibe) is initiated in patients treated or about to begin treatment with a statin.

Health care professionals should be aware that the use of Ezetrol® (ezetimibe) in combination with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations of liver transaminases.

Care should be exercised in the use of Ezetrol® (ezetimibe) in patients with active liver disease or unexplained persistent elevations of liver transaminases.

Adverse pancreatic events:

Physicians should consider the diagnosis of pancreatitis in patients who develop sudden acute abdominal pain during therapy with Ezetrol® (ezetimibe).

Suspected interaction between Ezetrol® (ezetimibe) and warfarin:

Additional International Normalized Ratio (INR) measurements are recommended in patients treated with warfarin, and in whom Ezetrol® (ezetimibe) is initiated.

The identification, characterization, and management of marketed health product-related adverse reactions are dependent on the active participation of health care professionals in adverse reaction reporting programmes. Any occurrences of muscle, hepatic, pancreatic, hematologic, suspected interaction with warfarin or other serious and/or unexpected adverse reactions in patients receiving Ezetrol® (ezetimibe) should be reported to Merck Frosst/Schering Pharmaceuticals or Health Canada at the following addresses:

Merck Frosst/Schering Pharmaceuticals
Attention: Director, Medical Services
P.O. Box 1005,
Pointe-Claire-Dorval,
Québec,
H9R 4P8

Any suspected adverse reaction can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866 234-2345
Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

For other inquiries, please refer to contact information:
Marketed Health Products Directorate
E-mail: mhpd_dpsc@hc-sc.gc.ca
Tel.: (613) 954-6522
Fax: (613) 952-7738

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.html
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adr_guideline_e.html

Your professional commitment to the informed use of Ezetrol® (ezetimibe) represents an important contribution to the protection of patients' well-being through the early recognition of potentially serious adverse events by patients.

Patient safety is of paramount importance to Merck Frosst/Schering Pharmaceuticals. We routinely review data from completed studies and clinical use of our products.

Should you have any questions or require additional information concerning the use of Ezetrol® (ezetimibe), please contact Merck Frosst/Schering Pharmaceuticals at 1-800-567-2594 from 8:30 am to 5:30 pm, Eastern Standard Time, Monday to Friday.

Sincerely,

original signed by

François Bertrand, M.D.
Executive Director, Medical Research

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References:

[1] Simard D, Turgeon J. The pharmacokinetics of ezetimibe. Can J Clin Pharmacol 2003;10 suppl A: 13A.