## EZETIMIBE

**Generic (Trade Name):** Ezetimibe (Zetia™)

**Manufacturer:** Schering-Plough

**Indication:** As monotherapy or in combination with statins for the reduction of elevated cholesterol levels (hypercholesterolemia).

**Current Regulatory Status:** In December 2001, a new drug application was filed with the FDA for the above indications. The status of this medication in Canada is currently unknown although it is expected that further filings outside the U.S. will be made during the first half of this year. Schering-Plough Corporation has entered a joint venture with Merck & Company to market a single tablet containing both Zetia (ezetimibe) and Zocor (simvastatin); this is only in the early phase of development at the time of review.

**Description:** Cholesterol control has been on the minds of both patients and practitioners, as clinical evidence has shown that regulation of the lipid profile can prevent outcomes such as cardiovascular events. Cholesterol concentrations are regulated in the body via two mechanisms; the endogenous pathway, where cholesterol is synthesized in extrahepatic/hepatic tissues, and the exogenous pathway, where dietary and biliary cholesterol is absorbed. Medications currently available exploit these paths to regulate plasma cholesterol levels. Ezetimibe is the first agent in a new class of medications, the selective cholesterol absorption inhibitors. It acts by inhibiting the intestinal absorption of both dietary and biliary cholesterol. It undergoes enterohepatic recycling, allowing it to be present at the site of action, the intestinal wall. As this agent differs in mechanism of action, it is theorized that when used in combination with other agents, it allows for synergism.

**Current Treatment:** In Canada, there are several classes of medications that can be used for the treatment of hyperlipidemia. Clinical guidelines have been published, including Canadian guidelines, that give recommendations regarding appropriate choices for therapy depending on the patient’s lipid profile. Lipid lowering therapies include bile acid sequestrants [cholestyramine resin (Questran™ - Bristol), colestipol hydrochloride (Colestid™ - Pharmacia)], fibrates [bezafibrate (Bezalip™ - HLR), clofibrate (generics), fenofibrate (Lipidil™ - Fournier), gemfibrozil [Lopid™ - Pfizer]], 3-hydroxy-3-methylglutaryl(HMG)-CoA reductase inhibitors [atorvastatin calcium (Lipitor™ - Pfizer), fluvastatin sodium (Lescol™ - Novartis), lovastatin (Mevacor™ - Merck), pravastatin sodium (Pravachol™ - BMS), simvastatin (Zocor™ - Merck)] and niacin (generics).

**Cost:** As this agent is not currently marketed, no cost can be supplied at this time.
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Evidence: Most of the data published in full at the time of review consists of either animal studies or phase I/II trials. There has been some preliminary data available in abbreviated or abstract form discussing phase III results. In 2001, the results of a phase III randomized, double-blind, parallel-group study were presented at the 72 annual meeting of the European Atherosclerosis Society. Patients (n=827) received ezetimibe 10 mg once daily or placebo for 12 weeks of therapy. At study end, compared to baseline, ezetimibe treated patients experienced a LDL-cholesterol levels decrease of 17.7 per cent, while those in the placebo group had an increase of 0.8 per cent (p < 0.01). Similarly, both the total cholesterol, HDL-C and triglyceride profile improved in the active-treatment arm, but worsened in the control group (p < 0.01, all three endpoints). Although the adverse effects noted in the trial were not stated, it was reported that ezetimibe was well tolerated.

Small scale, short-term or Phase I studies have shown favourable improvements in lipid profiles when ezetimibe has been combined with fenofibrate, fluvastatin, atorvastatin and simvastatin.

Commentary: The introduction of ezetimibe will add to the spectrum of lipid-lowering therapies. Particularly, concomitant use with statins is very attractive due to lack of interaction and the potential synergism. At this point, only short term efficacy data based on surrogate outcomes are available; further long term trials are necessary to assess the real impact of this medication on morbidity and mortality.

Although the data available to date suggest the drug is tolerable, pharmacovigilance will be necessary to monitor serious or life-threatening adverse events that could manifest with chronic use. The uncertainty surrounding potential harm from long-term use makes it a less attractive option for patients at a lower risk of cardiovascular events and death (e.g. in primary prevention). This agent has the potential to have a large impact in terms of both use and cost; industry analysts speculate ezetimibe to have sales of almost one billion by 2004.

References: Ezetimibe lowers LDL-cholesterol levels. Inpharma 2001;1291: 8.

Ezetimibe effective in primary hypercholesterolaemia. Inpharma 2001;1308:11.


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Cholesterol lowering agent ezetimibe (Zetia) filed for approval in US. DiZone News [database online].Available:http://www.druginfozone.org/news/May01/May01_news77/may01_news77.html


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

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Emerging Drug List
ISSN 1496-8398 (online only)