Healthy Skepticism
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July 2006 Australia

Lipidil™ (fenofibrate) (Solvay/Fournier)

Don't give him Lipidil… You may increase his risk of severe adverse effects without clinical benefit!

Beware important omissions! The FIELD study showed that Lipidil did not reduce cardiovascular and overall mortality in patients with diabetes

Beware surrogate endpoints! 'Proven to reduce coronary artery stenosis' may not mean improved clinical outcomes

L-C is a strong independent risk factor for coronary heart disease so effective t is essential. Lipidil (fenofibrate) is a fibric acid derivative that rais HDL-C regardless of ine levels[2] and has been proven to reduce coronary-artery stenosis in patients with type 2 diabetes.[3] Lipidil has been used by millions of patients worldwide and is generally well tolerated.[4-6]

For this sort of patient, make Lipidil the usual treatment.

LIPIDIL
fenofibrate 160 mg Once Daily

PBS Information: Restricted benefit. For use in patients that meet the criteria set out in the General Statement for Lipid-Lowering Drugs.

Please review the full product information. Full product information is available on request from Fournier Pharma. Indications: Adjunct to diet in the treatment of hypercholesterolaemia, types II, III, IV and V dyslipidaemia, dyslipidaemia associated with type 2 diabetes. Contraindications: Children, liver or severe renal dysfunction, existing gallbladder disease, hypersensitivity to fibrates or ketoprofen. Precautions: Diet and lifestyle modifications should be attempted prior to initiating therapy. Renal impairment: adjust dose according to creatinine clearance, see full PI. May increase LFTs. Cholelithiasis, myopathy, pancreatitis, use of oestrogens, pregnancy category B3, lactation. Interactions: Oral anti-coagulants, HMG-CoA reductase inhibitors and other fibrates, cyclosporin (monitor renal function), phenylbutazone, other concomitant medications especially those metabolized by cytochrome P450 CYP2C19, CYP2A6, and CYP2C9. Adverse reactions: Generally infrequent, mild and transient. Most common: gastrointestinal disorders (abdominal pain, nausea, vomiting, diarrhoea, flatulence), and skin reactions (rashes, pruritus, urticaria and photosensitivity reactions). Less frequent reactions: raised LFT, muscle toxicity and very rarely rhabdomyolysis, others see PI. Dose: Fenofibrate is presented as a 160 mg tablet and a 67 mg capsule. The usual dose of fenofibrate is 1 x 160 mg tablet to be taken with food. The 67 mg capsules are only recommended in renal impairment (CrCl <60ml/min): see full PI. Presentation: 67 mg capsules: Yellow, hard gelatin capsules. Packs of 60 capsules in blisters. 160 mg tablets: White, oblong, film-coated tablets. Packs of 30 tablets in blisters. PBS Dispensed Price: for 67 mg capsule $28·10 and 160 mg tablet $39·79. References: 1. National Institutes of Health, National Heart Lung and Blood Institute. NIH Pub No. 01-3670, May 2001. www.nhlbi.nih.gov/about/ncep/index.htm. 2. Poulter N. Br J Cardiol 1999;6(12):682-685. 3. Diabetes Atherosclerosis Intervention Study Investigators. Lancet 2001;357:905-910. 4. Data on file, Fournier Australia. 5. Approved Product Information for Lipidil. 6. Jones PH, Davidson MH. Am J Cardiol 2005;95:120-122. Lipidil is a registered trademark of Laboratories Fournier SA, ABN 47 080 087 538. Suite 7, Level 4, 35 Spring Street, Bondi Junction, NSW 2022. Telephone 02 9389 8611. Solvay Pharmaceuticals, division of Solvay Biosciences Pty. Ltd. Level 1, Building 2, 20 Bridge Street, Pymble NSW 2073. Telephone (61 2) 9440 0977. ABN 41 007 401 201. (FPA 5336) (SOLCODE: 150805-24)

SOLVAY PHARMACEUTICALS FOURNIER PHARMA

Lipidil™ (fenofibrate) is a member of the fibrate class of lipid level modifying drugs. It is registered in Australia for the treatment of dyslipidaemia and hypercholesterolemia. This advertisement, published in the April 2006 issue of *Medicines Today* (Australia), could be interpreted as promoting Lipidil™ as 'usual treatment' for people with type 2 diabetes.

Beware surrogate endpoints!

Solvay/Fournier, the drug company that markets Lipidil™ in Australia, claims that Lipidil™ '*has been proven to reduce coronary artery stenosis in patients with type 2 diabetes*', based on a study published in 2001 in *The Lancet*.[1] In this double-blind trial, 731 patients with type 2 diabetes were randomly assigned fenofibrate (200 mg/day) or placebo for at least 3 years. The extent of coronary stenosis was assessed by angiograms at the beginning and end of the trial. The fenofibrate group showed a significantly smaller increase in percentage diameter stenosis than the placebo group and a significantly smaller decrease in minimum lumen diameter, but the trial was not powered to examine clinically important endpoints such as heart attacks.

Coronary stenosis is a surrogate endpoint for coronary events. Surrogate endpoints are physiological, biochemical, radiological or other outcome measures distinct from 'clinically important' endpoints. Clinical trials evaluating surrogate endpoints require smaller sample sizes and can often be completed in weeks or months rather than years. However, using surrogate endpoints can lead to incorrect conclusions[2]. For example, post-menopausal hormone replacement improved a surrogate endpoint – lipid levels – and this change misled people to falsely believe that these hormones would reduce a clinically important endpoint – heart attacks.[3]

Omission of the most relevant information!

There is no mention in the advertisement of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study which was published in the *Lancet* in November 2005.[4] This randomised double-blind controlled trial assessed the efficacy of fenofibrate (200 mg/day) versus placebo in 9795 people with type 2 diabetes. Only 22% had previous cardiovascular disease. After 5 years, there was no statistically significant difference between fenofibrate and placebo in terms of total mortality (7.3% for fenofibrate versus 6.6% for placebo), coronary mortality (2% in both groups), coronary events (6% for fenofibrate versus 5% for placebo).

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[1] Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet. 2001 Mar 24;357(9260):905-10. PubMed

[2] Fleming, T. R. & DeMets, D. L. Surrogate end points in clinical trials: Are we being misled? Ann Intern Med. 1996;125(7):605-13. PubMed

[3] Fugh-Berman A, Pearson C. The overselling of hormone replacement therapy. Pharmacotherapy. 2002 Sep;22:1205-8. PubMed

[4] Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al.; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): a randomised controlled trial. Lancet. 2005 Nov 26;366(9500):1849-61. PubMed

Severe adverse effects were reported more frequently with fenofibrate (0.8% versus 0.5% for placebo), in particular more pancreatitis, pulmonary embolism and deep vein thrombosis. The Medicines Australia (2002) Code of Conduct prohibits misleading by omission (p. 12).[5]

Are all fibrates equivalent?

In 2003, Lipidil™ was listed on the Australian Schedule of Pharmaceutical Benefits. The basis for this decision was that its lipid-modifying effect was comparable to that of another fibrate, gemfibrozil, i.e. there is a class effect common to all fibrates. However, unlike fenofibrate, gemfibrozil has been shown to reduce coronary mortality in patients with previous coronary disease.[6]

We have written to the Chair of the Pharmaceutical Benefits Advisory Committee, to ask the Committee to remove Lipidil™ from the list of drugs that are subsidised by the Australian Government.

Statins are considered first-line treatment for people with diabetes.[7] The FIELD study has shown that fenofibrate does not provide a safe and effective alternative to statins. Fenofibrate has no place in the prevention of cardiovascular disease in patients with diabetes.

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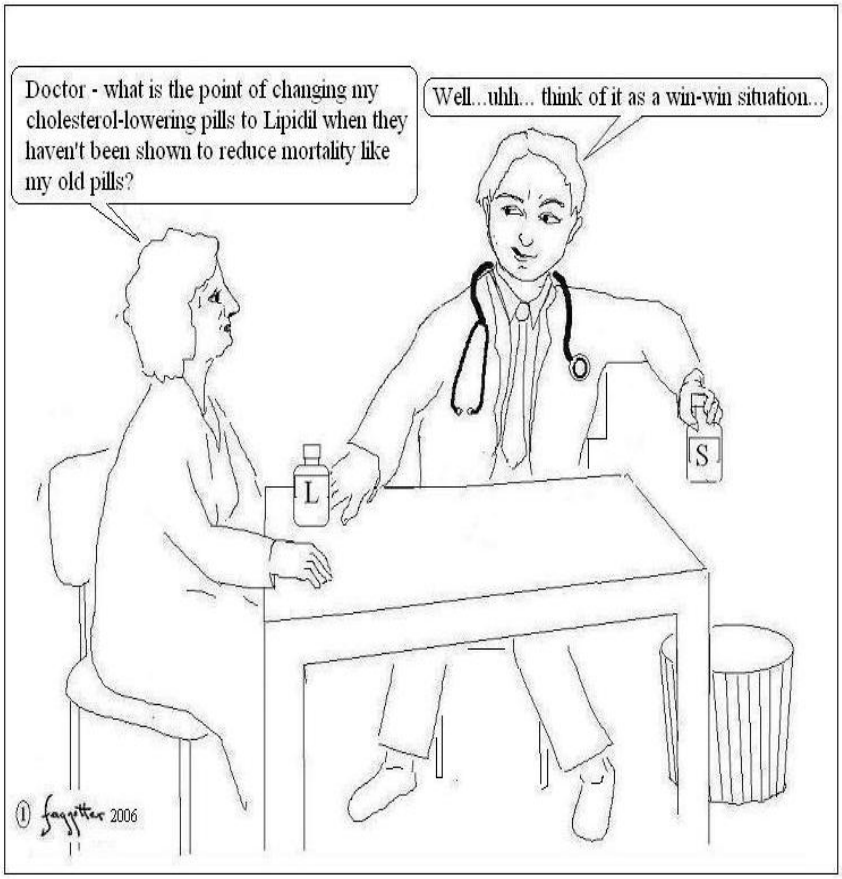
[5] Medicines Australia. Code of Conduct. 14th ed. Deakin ACT (Australia): Medicines Australia; 2002. Link

[6] Rubins HB, Robins SJ Collins D. Nelson DB, Elam MB, Schaefer EJ, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med. 2002;162(22):2597-604. PubMed

[7] Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. BMJ. 2006;332(7550):1115-24. PubMed


Doctor - what is the point of changing my cholesterol-lowering pills to Lipidil when they haven't been shown to reduce mortality like my old pills?
Well...uhh... think of it as a win-win situation...
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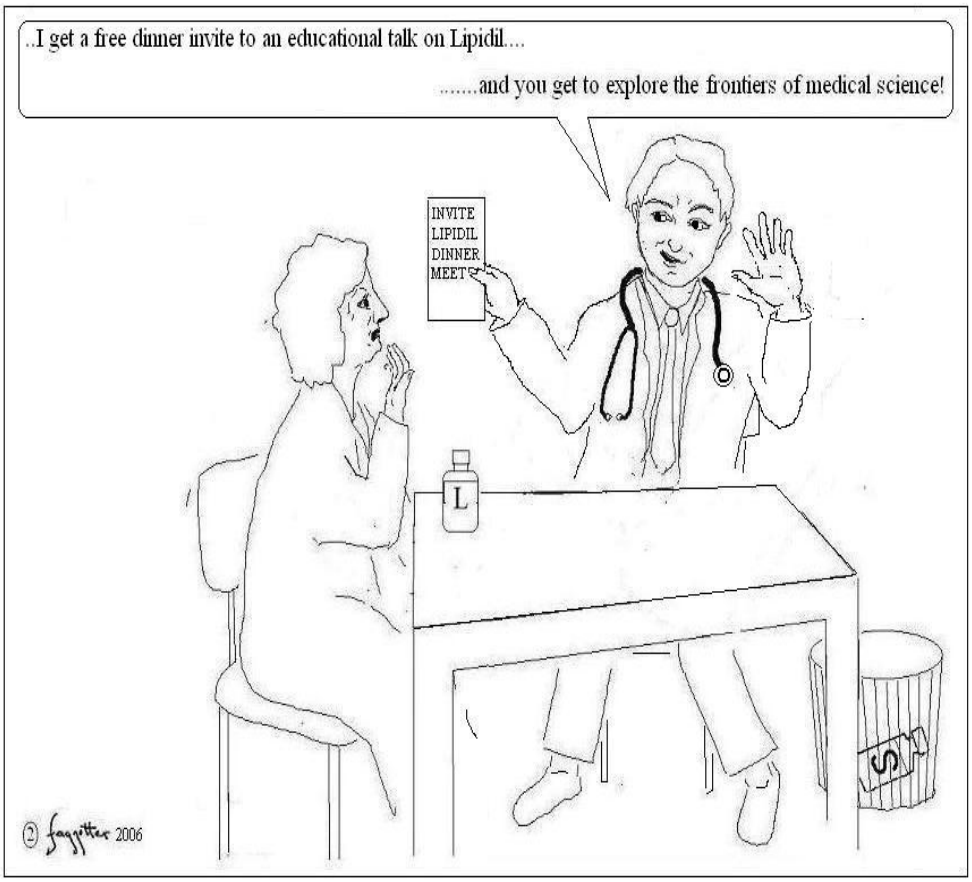
..I get a free dinner invite to an educational talk on Lipidil....
.....and you get to explore the frontiers of medical science!
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