NPS RADAR
Rational Assessment of Drugs and Research

Fenofibrate (Lipidil) for dyslipidaemia

(fen-o-FIE-brate)

Summary

- Statins are first line for people with existing cardiovascular disease.
- Fenofibrate is an alternative to gemfibrozil in hypertriglyceridaemia, or in mixed dyslipidaemia when elevated triglyceride concentration is the predominant disorder.
- Monitor for myopathy when fenofibrate is used in combination with a statin, as the risk is increased.

PBS Listing

Restricted benefit

For use in patients who meet the criteria set out in the General Statement for Lipid-Lowering Drugs in the *Schedule of Pharmaceutical Benefits*.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended listing fenofibrate on the basis of cost minimisation compared with gemfibrozil. Equi-effective doses were gemfibrozil 1200 mg and fenofibrate 160 mg (tablet formulation).[1]

The economic analysis was based largely on an unpublished 24-week study comparing the lipid-modifying efficacy of fenofibrate and gemfibrozil in 234 people with mixed dyslipidaemia (see *Place in therapy*).[2] The PBAC considered that the study did not provide conclusive evidence of a clinically important advantage for fenofibrate over gemfibrozil and so recommended listing on the basis of equivalent efficacy and cost to those for gemfibrozil.

Place in therapy

Fenofibrate is a member of the fibrate class of lipid-modifying drugs. It has been available in other countries since 1975 but has only recently been registered in Australia. Gemfibrozil is the other fibrate available in Australia.

A fibrate should be used first line, after lifestyle modification, in hypertriglyceridaemia.

In mixed dyslipidaemia, a fibrate can be used first line when elevated triglyceride concentration is the predominant abnormality. However, for people with existing cardiovascular disease (including those with diabetes and evidence of vascular disease), statins are recommended first line because they have more evidence of benefit (see *FIELD study results do not change recommendations*).[3,4] Combination therapy may be required when both low-density lipoprotein–cholesterol (LDL-C) and triglyceride concentrations are moderately to markedly elevated. Note that the combination of a statin and a fibrate increases the risk of myopathy; specialist advice may be required (see *Safety issues*).

In hypercholesterolaemia, a fibrate could be considered if other LDL-C-lowering drugs (statins, bile-acid-binding resins or nicotinic acid) are not tolerated. Statins are the agents of choice in hypercholesterolaemia because they are the most potent LDL-C-lowering drugs and are supported by clinical outcome evidence.[5]

For more information about drug choices in dyslipidaemia, refer to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand *Lipid Management Guidelines 2001* and *Position statement on lipid management — 2005*, the *Australian Medicines Handbook* or *Therapeutic Guidelines: Cardiovascular*.[5–8]

FIELD study results do not change recommendations

The results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study do not change previous recommendations for using lipid-modifying drugs in people with diabetes.[9] The FIELD study did not find that fenofibrate was superior to placebo in reducing the risk of coronary events in people with type 2 diabetes (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.75 to 1.05, p = 0.16). The primary endpoint was a composite of death due to coronary heart disease, the risk of which was non-significantly elevated in the fenofibrate group (HR 1.19, 95% CI 0.90 to 1.57, p = 0.22), and non-fatal myocardial infarction, the risk of which was significantly reduced (HR 0.76, 95% CI 0.62 to 0.94, p = 0.01). Trial participants had baseline plasma total cholesterol concentrations of 3.0–6.5 mmol/L plus either total/HDL–cholesterol ratios of 4 or more, or plasma triglyceride concentrations of 1–5 mmol/L. Apart from those with existing coronary heart disease, many participants would not have fulfilled the current PBS criteria for subsidised fenofibrate.

Lifestyle changes are first line

To reduce overall cardiovascular risk, manage all modifiable risk factors. Patients should make diet and lifestyle changes before starting drug therapy and continue them adjunctively.

In people with diabetes, optimise glycaemic control to improve the lipid profile.

Fenofibrate compared with gemfibrozil

Like other fibrates, fenofibrate reduces triglyceride concentration by 20–50%.[10] In isolated hypercholesterolaemia, reductions in LDL-C concentrations of up to 25% have been reported with fenofibrate.[11] Fibrates tend to elevate LDL-C concentration in hypertriglyceridaemia.[3]

There is little evidence that fenofibrate has greater lipid-modifying efficacy than gemfibrozil. The efficacy of micronised* fenofibrate and gemfibrozil has been directly compared in only one randomised controlled trial in 234 patients with mixed dyslipidaemia but this study has not been published.[2] There were no statistically significant differences between gemfibrozil and fenofibrate in effects on triglyceride, HDL-C and measured LDL-C concentrations. There were statistically significant differences in favour of fenofibrate for total cholesterol:HDL-C ratio, and total cholesterol and calculated LDL-C concentrations. However, these differences were small and may not correspond to a clinically meaningful advantage.

There are no randomised controlled trials evaluating the effects of fenofibrate in people who fail to achieve lipid goals using gemfibrozil. However, individual responses to drugs can differ, so an inadequate response to one fibrate does not preclude a trial of the other.

Safety issues

The adverse-effect profile of fenofibrate is well characterised because there has been considerable overseas clinical experience since it was first marketed in 1975.[12] Fenofibrate is generally well tolerated. The most commonly reported side effects are gastrointestinal (nausea, vomiting, diarrhoea, flatulence, abdominal pain) and dermatological (rash, pruritus, urticaria, photosensitivity reactions).[13]

During 5 years of follow up in the FIELD study, some serious adverse events occurred more commonly in people taking fenofibrate than in those taking placebo, including pulmonary embolism (1% vs 0.7%, p = 0.022), deep vein thrombosis (1.4% vs 1%, p = 0.074) and pancreatitis (0.8% vs 0.5%, p = 0.031). It is not known if there is a causal association between fenofibrate and thromboembolic events. Plasma creatinine concentration was 10–12 micromol/L higher in the fenofibrate group than in the placebo group and returned to baseline levels when fenofibrate was stopped; it is not known whether this difference is clinically important. Three cases of rhabdomyolysis occurred in the fenofibrate group; none of these patients was taking a statin.[9]

Elevated serum transaminase concentrations may occur with fenofibrate: liver function monitoring is recommended every 3 months for the first 12 months of therapy. Treatment should be stopped if transaminase concentrations are elevated to more than three times the upper limit of normal.[13]

* The smaller particle size in micronised fenofibrate improves bioavailability, so lower doses are required than for non-micronised fenofibrate, which is available in other countries.

Myopathy is a possible, although rare, side effect of fibrates. The risk of myopathy during fibrate treatment is increased by concomitant statin use (see *Monitor for myopathy when used in combination with a statin*).

Report adverse events to the Adverse Drug Reactions Advisory Committee online (see www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with the *Schedule of Pharmaceutical Benefits* and *Australian Prescriber*. For information about adverse event reporting, see the Therapeutic Goods Administration website (www.tga.gov.au).

Monitor for myopathy when used in combination with a statin

The combination of a statin and a fibrate should be reserved for people in whom the benefits are likely to outweigh the risks, such as those with severe mixed dyslipidaemia who are at high cardiovascular risk. People at higher risk of myopathy include older people, women and those with diabetes or chronic renal failure. Taking high statin doses or other drugs that interact with statins (such as macrolide antibiotics, some azole antifungals and cyclosporin) also elevates the risk of myopathy.[14,15]

Patients should be advised to report any unexplained muscle pain or weakness, and creatine kinase levels should be measured if symptoms suggest myopathy. Specialist advice may be needed.

Fenofibrate combined with a statin may be associated with a lower risk of rhabdomyolysis than gemfibrozil combined with a statin. A comparison of adverse event reporting rates found that the use of gemfibrozil with a statin was associated with more reports of rhabdomyolysis per million prescriptions than the use of fenofibrate with a statin (8.6 vs 0.58 cases reported per million prescriptions*).[16] Nonetheless, be aware that the risk of myopathy is increased when combining a statin with fenofibrate.

Dosing issues

Fenofibrate is available as 160 mg tablets and 67 mg capsules. The bioavailability of the tablet and capsule formulations differs, so 3 capsules (i.e, 200 mg of the capsule formulation) are equivalent to 1 tablet.

The recommended daily dose is 1 x 160 mg tablet. There is no advantage in daily doses higher than 160 mg.

The capsules can be used when lower doses are required, such as for people with renal impairment.

Information for patients

Advise patients to promptly report unexplained muscle pain or weakness, especially if taking fenofibrate in combination with a statin.

Ensure that they understand that they should not combine fenofibrate tablets and capsules.

Discuss the importance of lifestyle changes in reducing overall cardiovascular risk. Information about lifestyle changes for patients is available from the Heart Foundation's national telephone information service, *Heartline* (phone 1300 36 27 87) or online (www.heartfoundation.com.au).

The Lipidil consumer medicine information (CMI) is included in the pack.

* Excluding cases in which a fibrate was used in combination with cerivastatin.

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