

drug information perspectives

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Fenofibrate

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FENOFIBRATE

SYNONYM: Procetofen

TRADE NAMES: Apo-Fenofibrate, Apo-Feno-Micro, Dom-Fenofibrate Micro, Feno-Micro, Gen-Fenofibrate Micro, Lipidil EZ, Lipidil Micro, Lipidil Supra, Novo-Fenofibrate Micronized, PHL-Fenofibrate Micro, PMS-Fenofibrate Micro, Ratio-Fenofibrate MC

CLASSIFICATION: Lipid-modifying; third-generation fibrate

ACTION

PPAR-alpha (peroxisome proliferator activated receptor-alpha) agonist. PPAR-alpha controls the transcription of genes that regulate fatty acid and cholesterol metabolism. Hepatic synthesis of triglycerides is reduced, probably by increased hepatic fatty acid oxidation, lipoprotein lipase activity is increased, and triglyceride clearance is enhanced. Decreases triglycerides and increases HDL; LDL may decrease or increase. Structurally related to clofibrate. May also reduce atherosclerotic events by reducing postprandial lipemia, inhibiting angiogenesis, reducing fibrinogen levels, reducing Lp(a) and promoting larger, less dense LDL particles. Reduces serum uric acid levels by increasing its urinary excretion independent of lipid effects.

PHARMACOKINETICS

- **Half-life:** 19-27 hours.

- **Absorption:**

Non-micronized: poor and variable absorption, administration with food increases absorption to 60% of a dose.

Micronized form (Lipidil Micro): better and less variable absorption than non-micronized form, but oral absorption is still poor; increased 35% if given with food.

Microcoated-micronized form (particles coated with micronized fenofibrate; suprabioavailable; Lipidil Supra): Improved and more predictable absorption than micronized form; slightly enhanced absorption if given with a meal.

Nanocrystallized form (Lipidil EZ): best absorption, not altered if given with food or in fasting state.

- **Distribution:** >99% protein bound. Mostly distributed to liver, kidney and GI tract.

- **Metabolism:** Absorbed fenofibrate is rapidly and completely hydrolysed to the active form, fenofibric acid, by tissue and plasma esterases. Not significantly metabolized by P450 enzymes.

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- **Elimination:** Mainly renal (60-88% in urine as the active metabolite and glucuronidated forms, 5-25% in feces as unchanged fenofibrate).
- **Special populations:** **Elderly:** half-life is prolonged. **Renal function impairment:** reduced clearance and 3-20-fold increased half-life. Not removed by hemodialysis. **Hepatic impairment:** half-life increased to 44-56 hours; a compensating change occurs in the volume of distribution.

USES AND EFFICACY

Uses: An adjunct to diet in the treatment of **dyslipidemia**, especially to reduce triglyceride levels and to raise HDL-cholesterol levels. Used in patients with familial hypercholesterolemia, familial combined dyslipidemia, dysbetalipoproteinemia, and familial hypertriglyceridemia (Frederickson Type IIa, IIb, III, IV and V dyslipidemia). Reduces triglyceride levels by 20-63%, with a greater percent reduction with higher baseline triglyceride levels. Reduces LDL levels by 2-30%, although LDL may increase as much as 30-45% in Types IV and V dyslipidemia. Increases HDL levels by 0-22%.

Major Clinical Trials

DAIS (Diabetes Atherosclerosis Intervention Study) 2001: Patients (n=418) with well-controlled type 2 diabetes and mild typical lipoprotein abnormalities were randomly assigned to either fenofibrate or placebo for 3 years. Half of the patients had a history of clinical coronary disease. Patients given fenofibrate had significantly less progression of focal coronary artery lesions than those given placebo. The beneficial effect of fenofibrate was associated with a large reduction in triglyceride levels, slight increase in HDL, slight reduction in LDL, and increased LDL particle size. Limitation: Although this demonstrates a reduction in the progression of coronary artery disease in type 2 diabetics, the study was not sufficiently large to evaluate clinical outcomes.

FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) 2005: A randomized, double-blind, placebo-controlled trial of the effects of fenofibrate on diabetic cardiovascular events followed 9795 patients with type 2 diabetes (mainly white male patients; at start, no lipid-modifying therapy, 59% low HDL, 52% high triglycerides, 38% both, 22% prior cardiovascular disease, 56% hypertension). As the study progressed, many patients added statin drugs. After five years, patients given fenofibrate had reduced triglyceride levels by 22% (27% if no statin), lower LDL levels by 6% (15% if no statin) and increased HDL levels 1.2% (2% if no statin). Effects on cardiovascular disease were mixed. There was a nonsignificant 11% reduction in the primary outcome measure, nonfatal MI plus coronary heart disease events, in the fenofibrate group. Fenofibrate produced a statistically significant 11% reduction in total cardiovascular events, due to a 25% reduction in nonfatal MI and a decrease in revascularization. However, there was a nonsignificant increase in mortality from coronary heart disease (19%) and in all cause cardiovascular death (11%). The rate of progression of albuminuria was significantly lower in the fenofibrate group, suggesting a benefit in microvascular disease. Limitations: Statin drugs were added, especially in the placebo group, which may have reduced the treatment effect difference. Effects on LDL and HDL were modest.

SAFARI 2005: A multicentre, randomized, double-blind trial compared simvastatin monotherapy with combined simvastatin plus fenofibrate in 618 patients with combined hyperlipidemia. Approximately 70% of the patients had metabolic syndrome. After 12 weeks, combined statin plus fibrate therapy resulted in significantly greater effects on triglyceride levels (43% reduction vs. monotherapy 20%), HDL (19% increase vs. monotherapy 10% increase), and LDL (31% reduction vs. monotherapy 26%). Combination therapy also shifted the LDL particle pattern towards less atherogenic larger and more buoyant particles. Creatine kinase levels increased in one patient given combination therapy and none given monotherapy. Limitations: More study is needed to determine if the lipid changes and slight added reduction in LDL cholesterol translate into reduced cardiovascular events or mortality. This study is too short and small to assess the safety of long-term combined therapy.

Clinical course: Rapid effect, with maximum benefit on triglycerides and other lipids within two weeks.

Place in Therapy

Fibrates are the most effective drugs for lowering high triglyceride levels. Fenofibrate has not been shown to improve clinical outcomes, although other drugs in this class have (see gemfibrozil), and fibrates have not been proven to reduce total mortality. Fibrates are among the drugs of first choice in patients with (1) severely elevated triglyceride levels with a risk of pancreatitis, (2) dysbetalipoproteinemia (Type III dyslipidemia), and (3) patients with high triglyceride levels and low HDL. Studies indicate that patients with low HDL benefit from fibrate drugs, as do those with type 2 diabetes with the typical dyslipidemia of high triglycerides, low HDL and small, dense, atherogenic LDL particles (although statin-induced LDL lowering is the initial concern), and the metabolic

syndrome, as they are more likely to normalize triglyceride and HDL levels than a statin. For patients with common mixed hypercholesterolemia (types IIa and IIb), statins are first choice drugs since they are more effective at reducing LDL levels, and have been shown to reduce CHD. For mixed hypercholesterolemia involving predominantly high triglyceride levels (Type IIb), statins or fibrates are recommended. Compared with other fibrates, the magnitude of fenofibrate's effects on triglycerides and HDL is similar to that of bezafibrate and gemfibrozil; fenofibrate may have slightly stronger effects on LDL and triglycerides; patients who do not respond fully to gemfibrozil 1200mg/day may achieve better results with fenofibrate. Compared with statin drugs, fenofibrate has a more beneficial effect on triglycerides and HDL but less effect on LDL. Compared with niacin, it is slightly more effective for high triglycerides but less effective for raising HDL, and avoids niacin's potential to raise blood glucose and cause flushing.

Advantages

- Lack of interactions involving P450 enzymes.
- Larger reduction in triglycerides in patients with higher baseline levels, e.g. Type IIb, Type IV.
- Does not raise blood glucose.
- Available in a dosage form that can be given once daily without regard to meals.

Disadvantages

- Limited data on clinical outcomes.
- The magnitude of the lipid effect is variable.
- LDL may increase in some patients, e.g. Type IV or V dyslipidemia.
- Raises levels of homocysteine, an independent risk factor for atherosclerosis (unlike gemfibrozil).

Investigational/unapproved Uses

- **Gout:** Reduces serum uric acid 15-35%; remission of gout attacks for several years has been reported in a few cases; a possible alternative if other drugs are ineffective or the patient also has dyslipidemia.
- **Lypodystrophy syndrome in patients with HIV:** Reduces triglyceride levels as well as improving the atherogenic lipid profile, but does not improve the fat redistribution syndrome.
- **Chylomicronemia (type I dyslipidemia; lipoprotein lipase deficiency):** Usually managed with a low-fat diet, but fibrates have been used clinically.
- **Type 2 diabetes:** The results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, designed to determine the cardiovascular benefits of tight glycemic control, statin, fibrate and antihypertensive therapy in type 2 diabetes, are expected in 2010.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications

- **Hypersensitivity** or history of adverse reaction to fenofibrate.
- **Severe renal impairment** (reduced elimination).
- **Hepatic impairment** including primary biliary cirrhosis (altered pharmacokinetics and liver function possible).
- **Gallbladder disease** (gallstones can occur).
- **Pregnancy** (animal data suggest risk; cholesterol-lowering not needed).
- **Lactation** (animal data suggest risk; cholesterol-lowering not appropriate).
- **Photoallergy or phototoxicity from fibrates or ketoprofen** (cross-sensitivity possible).
- **Chylomicronemia** (type I dyslipidemia with normal VLDL levels; contraindicated by manufacturer; usually ineffective).

Precautions

- **Monitor liver function** after 3-6 months and then annually (increased transaminase levels reported).
- **Statin drugs** (increased risk of rhabdomyolysis and acute renal failure): avoid if possible, evaluating the risk vs. benefit, but always avoid if risk factors for myopathy exist: age over 70, renal impairment, liver impairment, existing myopathy or history of prior myopathy with a fibrate, concurrent fibrates or ezetimibe, electrolyte imbalance, family history of muscle disorders, hypothyroidism, alcohol abuse, excessive physical exercise.
- **Children:** Other lipid-modifying drugs are usually preferred in children if required.
- **Report any unexpected or serious reactions** to Health Canada's adverse reaction monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789).

PREGNANCY AND LACTATION

Embryocidal and teratogenic when given to pregnant rats at 7-10 times the maximum recommended human dose. Not recommended in pregnancy because this animal data suggests risk, plus there is no need to treat cholesterol during pregnancy. Avoid breast-feeding because of carcinogenicity in animals (in rodents, doses 1-6 times the maximum human dose have been associated with hepatic and pancreatic cancer; neoplasms have been observed in the testes of mice). As well, newborns need cholesterol for proper development.

SIDE EFFECTS

Incidence is given in brackets.

Cardiovascular: Pulmonary embolism (1% vs placebo 0.7%); deep vein thrombosis.

Dermatologic: Rash (may be severe; rare Stevens-Johnson syndrome and toxic epidermal necrolysis).

Photosensitivity (photoallergy and phototoxicity; cross-sensitivity with ketoprofen due to a shared benzophenone structure; sensitive in the UVA and UVB ranges, onset several days).

Gastrointestinal: Constipation, diarrhea, dyspepsia, flatulence (3-5%).

Genitourinary: Increased serum creatinine.

Hematologic: Decreased hemoglobin, hematocrit, white blood cells (early onset, stabilizes with time).

Hepatic: Increased transaminase levels (5%, dose-related, may reverse despite drug administration); hepatitis.

Decreases serum alkaline phosphatase levels.

Musculoskeletal: Myopathy, increased creatine phosphokinase, rhabdomyolysis, acute renal failure (rare, can occur with monotherapy or in combination with statin drugs; risk factors: see PRECAUTIONS, DRUG INTERACTIONS).

Other: Gallstones (due to increased cholesterol saturation of bile). Pancreatitis (0.8% vs placebo 0.5%). Increased homocysteine levels (independent risk factor for atherosclerosis, 50% increase, may be reduced by administration of folic acid). In rodents, doses 1-6 times the maximum human dose have been associated with hepatic and pancreatic cancer; neoplasms have been observed in the testes of mice.

INTERACTIONS

DRUG	EFFECT	MECHANISM	IMPORTANCE
Acenocoumarol	Bleeding risk	Unknown	Reduce dose of acenocoumarol, monitor INR
Cholestyramine	Reduced absorption of fenofibrate	Adsorption	Wait 2 hours between administration
Colestipol	Reduced absorption of fenofibrate	Adsorption	Wait 2 hours between administration
Cyclosporine	Myopathy, renal impairment, decreased cyclosporine levels	Unknown	Caution
Ezetimibe	Myopathy, increased ezetimibe absorption, increased gallstone risk	Unknown; increased cholesterol in bile	Avoid (no safety data), controversial
Rosiglitazone	Decreased HDL level	Unknown	Caution, monitor

Statin drugs	Myopathy, rhabdomyolysis; increased Cmax of pravastatin	Unknown	Avoid if possible
Warfarin	Bleeding risk	Unknown	Reduce warfarin dose initially by 1/3, monitor INR

Moderately inhibits CYP2C8 and 2C9, weakly inhibits 2A6 and 2C19, and inhibits P-glycoprotein in vitro. Lack of pharmacokinetic effect on: Repaglinide, rosuvastatin, simvastatin.

DOSAGE

Newer formulations have improved absorption of fenofibrate. Dosage equivalents (oldest to newest products):

Non-micronized fenofibrate 300mg given with food

= Micronized fenofibrate 200mg given with food, e.g. Lipidil Micro

= Micronized-microcoated fenofibrate 160mg, e.g. Lipidil Supra

= Nanocrystallized fenofibrate 3 doses of 48mg (145mg), e.g. Lipidil EZ.

Adults

Oral: Non-micronized capsules: 300mg per day in 2-3 divided doses with meals, or 200mg once daily.

Micronized capsules: 67-200mg daily.

Micronized-microcoated tablets (Lipidil Supra): 160mg daily. Maximum 200mg daily.

Nanocrystallized tablets (Lipidil EZ) 145 mg once daily without regard to meals. Maximum 145 mg daily.

Therapeutic trial: 3 months.

Elderly: Initial dose: Micronized capsules: 67mg daily. Nanocrystallized tablets (Lipidil EZ): 48mg, adjust based on response.

Children: Not approved: Oral: Non-micronized fenofibrate: 5mg/kg/day has been recommended in children over 10 years of age.

Renal impairment (mild-moderate): Reduce dose. Initially: Micronized capsules: 67mg/day. Or, micronized-microcoated (Lipidil Supra): 100mg daily. Or, nanocrystallized tablets (Lipidil EZ) 48mg daily. Adjust. Contraindicated in patients with severe renal failure or on dialysis.

Liver impairment: No data.

NURSING IMPLICATIONS

Most fenofibrate products will be better absorbed if given with food. The exception is Lipidil EZ, which will be well absorbed if given on an empty stomach or with food.

Watch for signs of myopathy (muscle weakness or pain), liver damage (nausea, anorexia, jaundice, pale stools, dark urine), or gallstones (severe stomach pain, nausea, vomiting). If these occur, inform the physician.

Encourage the patient to follow the diet that has been recommended.

PATIENT INSTRUCTIONS

Fenofibrate (fen-oh-FYE-brate) is given to reduce high triglyceride levels and improve other lipid levels.

Take this medication exactly as prescribed by your physician. If you are taking micronized fenofibrate, e.g. Lipidil Micro, or microcoated fenofibrate, e.g. Lipidil Supra, it is important to take your dose with food. Lipidil EZ may be taken with food or on an empty stomach.

If you have any of the following conditions, be sure that your prescribing physician is aware of that before you take this medication: liver disease, kidney disease, gallbladder disease, photosensitivity to this drug or to ketoprofen.

This medication is usually well tolerated. If you notice muscle pain or weakness, yellow skin, pale stools, dark urine, stomach or abdominal pain, nausea or vomiting, or any other unusual or annoying side effects, contact your physician.

Some patients develop sensitivity to the sun while taking this drug. Consider using a sunscreen that protects against UVA and UVB if you will be exposed to strong sunlight.

Birth control is recommended in women taking this product. If you are planning to become pregnant, discuss this with your physician. Discontinue fenofibrate several months before attempting to become pregnant. If you become pregnant while taking this drug, stop taking it and consult your physician.

Other drugs can interact with this medication. Make sure that your physician is aware of any other drugs you are taking.

Keep this medication in its original container, away from heat and moisture, and out of the reach of children.

If you have experienced any unexpected or serious reactions to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number. Also ensure that your physicians are informed and record this for the future.

PRESENTATION

Capsules:

Non-micronized:

Apo-Fenofibrate: 100mg.

Micronized:

Apo-Feno-Micro: 67, 200mg.

Dom-Fenofibrate Micro: 200mg.

Feno-Micro: 200mg.

PHL-Fenofibrate Micro: 200mg.

Riva-Fenofibrate Micro: 200mg.

Gen-Fenofibrate Micro 200mg.

Lipidil Micro: 200mg.

Novo-Fenofibrate Micronized: 67, 200mg.

PMS-Fenofibrate Micro 200mg.

Ratio-Fenofibrate: 200mg.

Tablets:

Micronized-microcoated, suprabioavailable: Lipidil Supra: 100, 160mg.

Nanocrystallized: Lipidil EZ: 48, 145mg.

References are available on request.