PT. Pfizer Indonesia
Local Product Document

Product Document Title : Gemfibrozil
Product Document No. : 515
Date : April 07, 2014
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NAME OF THE MEDICINAL PRODUCT

LOPID

DRUG PRESENTATION

Film Coated Tablet

COMPOSITION

Gemfibrozil 900 mg

DRUG LIST CLASSIFICATION

Prescription drug

USAGE

Oral

INDICATIONS

1. Primary prevention of coronary heart disease in 40- 55 year-old patients with hyperlipidemia who are unresponsive to diet.
2. Treatment of patients with hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia, or with Fredrickson's classification types IIa, IIb and IV so that it can prevent coronary heart disease.
3. Treatment of other hiperlipidemia:
   a. Fredickson types III and V.
   b. Diabetes-associated dyslipidemia.
   c. Dyslipidemia-associated xanthoma.

CONTRAINDICATIONS

- Patients with severe hepatic or renal dysfunction.
- Gallbladder disease.
- Hypersensitivity to Gemfibrozil or the drug component.
- The concomitant use of gemfibrozil with cerivastatin is also contraindicated.
- The concomitant use of gemfibrozil with repaglinide is contraindicated.

- The concomitant use of gemfibrozil with simvastatin is contraindicated (see sections **Special Warnings and Precautions for Use, Drug Interactions).**

DOSAGE AND ADMINISTRATION

- 600 mg twice a day, 30 minutes before breakfast and dinner.
- The 900 mg dosage is given to patients who are intolerant to normal dose.
- Maximum daily dose of 1500 mg can be given if the maximal decrease of triglyceride is needed, such as in type V patient.

ADVERSE REACTIONS

In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received gemfibrozil for up to five years. In that study, the following adverse reactions were statistically more frequent in subjects in the gemfibrozil group:

	Gemfibrozil (N = 2046)	Placebo (N = 2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal Pain	9.8	5.6
Acute appendicitis	1.2	0.6
Atrial fibrillation	0.7	0.1

Adverse events reported by more than 1% of subjects, but without a significant difference between groups:

	Gemfibrozil (N = 2046)	Placebo (N = 2035)
	Frequency in percent of subjects	
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Additional adverse reactions that have been reported where a causal relationship to treatment with gemfibrozil is probable are:

Body System SOC	Adverse Reaction
Hepatobiliary disorders	cholestatic jaundice

Gastrointestinal disorders	pancreatitis
Nervous System disorders	dizziness, somnolence, paresthesia, peripheral neuritis, headache
Psychiatric disorders	decreased libido, depression
Eye disorders	blurred vision
Reproductive system and breast disorders	impotence
Musculoskeletal and connective tissue disorders	arthralgia, synovitis, myalgia, myopathy, myasthenia, painful extremities, rhabdomyolisis
Skin and subcutaneous tissue disorders	exfoliative dermatitis, rash, dermatitis, pruritus, angioedema, urticaria
Respiratory, thoracic and mediastinal disorders	laryngeal edema
Blood and lymphatic system system disorders	severe anemia, leucopenia, thrombocytopenia, eosinophilia, bone marrow hypoplasia (see section **Special Warnings and Precautions for Use**)

Additional adverse reactions that have been reported included photosensitivity, alopecia, cholecystitis and cholelithiasis (see section **Special Warning and Precautions for Use**).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cholelithiasis

Gemfibrozil may increase cholesterol excretion into the bile raising the potential for gallstone formation. If cholestasis is suspected, gallbladder studies are indicated. The therapy with Gemfibrozil should be discontinued if gallstones are found. Cases of Cholelithiasis have been reported with gemfibrozil therapy.

HMG-CoA reductase Inhibitors

The concomitant administration of gemfibrozil with simvastatin is contraindicated. There have been reports of severe myositis with markedly elevated creatine kinase (CK) and myoglobinuria (rhabdomyolysis) when gemfibrozil and HMG-CoA reductase inhibitors were used concomitantly.

Anticoagulants

Caution should be exercised with concomitant use of warfarin. The dosage of warfarin should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin time determinations are advisable until it has been definitely determined that the prothrombin time has stabilized.

Laboratory Tests

Elevated liver function tests (LFTs) such as liver transaminases (aspartate transaminase [AST ; serum glutamic oxaloacetic transaminase (SGOT)], and alanine aminotransferase [ALT ; serum glutamic pyruvic transaminase (SGPT)), increased alkaline phosphatase, lactate dehydrogenase (LDH), CK, and bilirubin have rarely been reported with gemfibrozil administration. These are

usually reversible when gemfibrozil is discontinued. Therefore, periodic liver function studies are recommended, and gemfibrozil therapy should be terminated if abnormalities persist.

Hematopoietic
Mild decreases in hemoglobin, hematocrit and white cell have been observed occasionally on initiating gemfibrozil therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, eosinophilia and bone marrow hypoplasia have been reported. Therefore, periodic blood count determinations are recommended during the first 12 months of gemfibrozil administration.

Information for the Patient
The patient should be instructed to tell the physician if she is pregnant, a nursing mother, or thinking of becoming pregnant.

Patients taking gemfibrozil should be instructed about the importance of taking the drug under the prescribed regimen, about the importance of laboratory tests to monitor lipid levels and to report any experienced side effects.

Fertility, Pregnancy and Lactation
There are no adequate and well-controlled studies in pregnant women. The use of gemfibrozil in pregnancy should be reserved for those patients where the benefits clearly outweigh the risks to the patient or fetus.

Safety in nursing mothers has not been established. It is not known whether gemfibrozil is excreted in human milk. Since many drugs are excreted in human milk, the patient should discontinue nursing before beginning gemfibrozil therapy.

Effects on ability to drive and use machines
None known

DRUG INTERACTIONS

Anticoagulants
Caution should be exercised when warfarin is given in conjunction with gemfibrozil. The dosage of warfarin should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin time determinations are advisable until it has been definitely determined that the prothrombin time has stabilized.

HMG-CoA Reductase Inhibitors
The concomitant administration of gemfibrozil with simvastatin is contraindicated. There have been reports of severe myositis and myoglobinuria (rhabdomyolysis) when gemfibrozil and HMG-CoA reductase inhibitors, particularly cerivastatin (See section **Contraindications and Special Warnings and Precautions for use**), were used concomitantly.

Bile Acid - binding Resins
Reduced bioavailability of gemfibrozil may result when given simultaneously with resin-granule drugs such as colestipol. Administration of the drugs 2 hours apart or more is recommended.

Repaglinide
In healthy volunteers, co-administration with gemfibrozil increased the plasma concentration of repaglinide and prolonged its hypoglycemic effects. Co-administration of gemfibrozil and repaglinide increases the risk for severe hypoglycemia and is contraindicated (*see section* **Contraindications**).

Colchicine
Risk of neuromuscular toxicity and rhabdomyolysis may be increased with concomitant administration of colchicine and gemfibrozil. This risk may be increased in the elderly and in patients with hepatic or renal dysfunction. Symptoms usually last between 1 week and several months after colchicine withdrawal. Clinical and biological monitoring is recommended, especially at the start of combined treatment.

OVERDOSAGE

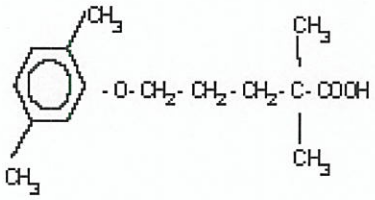
Overdosage has been reported with gemfibrozil. Symptoms reported with overdosage were abdominal cramps, abnormal LFTs, diarrhea, increased creatine phosphokinase (CPK), joint and muscle pain, nausea and vomiting . The patients fully recovered.

Symptomatic supportive measures should be taken should overdosage occur.

PHARMACOLOGICAL PROPERTIES

1. Pharmacodynamic properties

Gemfibrozil is a non-halogenated phenoxypentanoic acid with the following structural formula:



Molecular weight = 250.35
The chemical name is 5-(2, 5-dimethylphenoxy)-2, 2-dimethylpentanoic acid; the empirical formula is $C_{15}H_{22}O_3$.

Gemfibrozil is a white compound with a melting point of 58° to 61°C. Its solubility is 0.0019% in water and in acid and over 1% in dilute base. Gemfibrozil is stable under ordinary conditions.

Mechanism of Action

Gemfibrozil is a plasma lipid regulator that reduces total cholesterol, LDL, very-low-density lipoprotein (VLDL), and triglycerides and increases HDL cholesterol. The exact mechanism of action has not been clearly established yet. In human, gemfibrozil inhibits peripheral lipolysis and decreases hepatic extraction of free fatty acids. It also inhibits the synthesis and increases the clearance of apolipoprotein B, a carrier of VLDL, leading to the decrease in VLDL production. It also increases the HDL2 and HDL3 subfraction as well as apolipoprotein A1 and

A2. Animal studies suggest that the turnover and removal of cholesterol from the liver is increased by gemfibrozil.

2. Pharmacokinetic properties

Absorption - Gemfibrozil is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in 1 to 2 hours with a plasma half-life of 1.5 hours following multiple doses. Plasma levels appear proportional to the dose and do not demonstrate accumulation across time following multiple doses. Gemfibrozil pharmacokinetics are affected by the timing of meals relative to the time of dosing. In one study, both the rate and extent of absorption of the drug were significantly increased when administered 0.5 hour before meals. Average AUC was reduced by 14% to 44% when gemfibrozil was administered after meals compared to 0.5 hour before meals. In a subsequent study, rate of absorption of gemfibrozil was maximum when administered 0.5 hours before meals, with the C_{max} 50% to 60% greater than when given either with meals or fasting. In this study, there were no significant effects on the AUC of timing of dose relative to meals. (see section **DOSAGE AND ADMINISTRATION**).

Distribution –
Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other drugs. (see section **Special warnings and precautions for use**).

Metabolism –
Gemfibrozil undergoes oxidation of a ring methyl group to form successively a hydroxymethyl and a carboxyl metabolite.

Excretion –
Approximately 70% of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as the unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

3. Preclinical Safety Data

Carcinogenesis, Mutagenesis and Impairment of Fertility
There are no adequate, well-controlled studies in humans. Long-term studies have been conducted in rats at 0.2 and 1.3 times the human exposure (based on AUC). The incidence of benign liver nodules and liver carcinomas was significantly increased in high-dose male rats. In high dose female rats, there was a significant increase in the combined incidence of benign and malignant liver neoplasms.

A comparative carcinogenicity study was also done in rats comparing three drugs in this class: fenofibrate (10 mg/kg and 60 mg/kg; 0.3 and 1.6 times the human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

STORAGE
Store below 30°C, away from light.

SUPPLY
- Lopid 900 Film-Coated Tablet; Box, 3 blister @ 10 tablets; Reg. No.: DKL9619806517A1

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