LOPID®

1. TRADE NAME OF THE MEDICINAL PRODUCT

LOPID®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: gemfibrozil.

Each capsule contains 300 mg of gemfibrozil.

Each tablet contains 600 mg or 900 mg of gemfibrozil.

3. PHARMACEUTICAL FORM

Capsule

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Gemfibrozil is a lipid-regulating agent that is indicated for the following:

1. Treatment of adult patients with elevated levels of serum triglycerides (types IV and V hyperlipidemia), who present a risk of pancreatitis and do not respond adequately to a determined dietary effort to control them.
2. Primary prevention of coronary heart disease (CHD) and myocardial infarction (MI) in patients with hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia, Fredrickson's classification types IIa, IIb, and IV.
3. Treatment of other dyslipidemias:
   a. Fredrickson types III and V
   b. Associated with diabetes
   c. Associated with xanthomata

4.2 Posology and Method of Administration

General

Lipid levels should be measured on more than one occasion, to ascertain that the levels are consistently abnormal. Before instituting therapy with gemfibrozil, every attempt should be made to control serum lipids with appropriate diet, limiting alcohol intake, exercise, and weight loss in obese patients, as well as controlling other medical problems such as diabetes mellitus or hypothyroidism, which may contribute to the abnormal lipid levels. The patients should continue a standard cholesterol-lowering diet during treatment with gemfibrozil. Periodic determinations of serum lipids should be obtained during treatment with gemfibrozil. The drug should be withdrawn or additional therapy instituted if the lipid response is inadequate after 3 months.

The recommended daily dose is 900 mg to 1200 mg. The maximum daily dose is 1500 mg.

The 900 mg dose (gemfibrozil 900 mg tablet) is given as a single dose one-half hour before the evening meal. The 1200 mg dose (gemfibrozil 300 mg capsule or gemfibrozil 600 mg tablet) is given in two divided doses, one-half hour before the morning and evening meals (see section **5.2 Pharmacokinetic Properties**).

Use in Patients with Hepatic Dysfunction
See sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**.

Use in Patients with Renal Dysfunction
See sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**.

Use in Children
Safety and efficacy in children have not been established.

4.3 Contraindications

Gemfibrozil is contraindicated in patients with hepatic or severe renal dysfunction, pre-existing gallbladder disease, and in patients who are hypersensitive to gemfibrozil or any of the inert ingredients.

The concomitant use of gemfibrozil is contraindicated with any of the following:

- cerivastatin
- simvastatin

- rosuvastatin at 40 mg
- repaglinide
- dasabuvir
- selexipag

See sections **4.4 Special Warnings and Precautions for Use** and **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**.

4.4 Special Warnings and Precautions for Use

Cholelithiasis

Gemfibrozil may increase cholesterol excretion into the bile, raising the potential for gallstone formation. If cholelithiasis is suspected, gallbladder studies are indicated. Gemfibrozil therapy 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, as well as with rosuvastatin at 40 mg is contraindicated. Concomitant therapy of gemfibrozil with lower doses of rosuvastatin should be used only when the benefit outweighs the risks. 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, mostly notably cerivastatin (see section **4.3 Contraindications**). In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with HMG-CoA reductase inhibitors and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (see sections **4.3 Contraindications** and **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

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.

CYP2C8 Substrates

Gemfibrozil, an inhibitor of CYP2C8, may increase exposure of CYP2C8 substrates when administered concomitantly (see sections **4.3 Contraindications** and **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

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 (incidence <1/10,000), 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.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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, as well as with rosuvastatin at 40 mg is contraindicated. Concomitant therapy of gemfibrozil with lower doses of rosuvastatin should be used only when the benefit outweighs the risks. There have been reports of severe myositis and myoglobinuria (rhabdomyolysis) when gemfibrozil and HMG-CoA reductase inhibitors, particularly cerivastatin, were used concomitantly (see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**).

CYP2C8 Substrates

Gemfibrozil is an inhibitor of CYP2C8 and may increase exposure of drugs mainly metabolized by CYP2C8 (e.g., dabrafenib, enzalutamide, loperamide, montelukast, paclitaxel, pioglitazone, rosiglitazone) (see section **4.4 Special Warnings and Precautions for Use**). Therefore, dosing reduction of drugs that are mainly metabolized by CYP2C8 enzyme may be required when gemfibrozil is used concomitantly.

In healthy volunteers, co-administration with gemfibrozil increased the AUC and C_{max} of repaglinide by 8.1 fold and 2.4 fold, respectively. In the same study, co-administration with gemfibrozil and itraconazole increased the AUC and C_{max} of repaglinide by 19.4 fold and 2.8 fold, respectively. In addition, co-administration with gemfibrozil or with gemfibrozil and itraconazole prolonged its hypoglycemic effects. Therefore, co-administration of gemfibrozil and repaglinide increases the risk for severe hypoglycemia and is contraindicated (see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**).

Co-administration of gemfibrozil with dasabuvir increased dasabuvir AUC and C_{max} (ratios: 11.3 and 2.01, respectively) due to CYP2C8 inhibition. Increased dasabuvir exposure may increase the risk of QT prolongation, therefore, co-administration of gemfibrozil with dasabuvir is contraindicated (see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**).

Co-administration of gemfibrozil with selexipag doubled exposure (AUC) to selexipag and increased exposure (AUC) to the active metabolite, ACT-333679, by approximately 11-fold. Concomitant administration of gemfibrozil with selexipag is contraindicated (see section **4.3 Contraindications**).

In healthy volunteers given a single 160 mg dose of enzalutamide after gemfibrozil 600 mg twice daily, the AUC of enzalutamide plus active metabolite (N-desmethylenzalutamide) was increased by 2.2 fold and corresponding C_{max} was decreased by 16%. Increased enzalutamide exposure may increase the risk of seizures. If co-administration is considered necessary, the dose of enzalutamide should be reduced (see section **4.4 Special Warnings and Precautions for Use**).

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.

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.

***In-vitro* Studies of CYP Enzymes, UGTA Enzymes and OATP1B1 Transporter**

In-vitro studies have shown that gemfibrozil is an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, organic anion-transporting polypeptide (OATP) 1B1 and UDP-glucuronosyltransferase (UGT) 1A1 and 1A3 (see section **4.4 Special Warnings and Precautions for Use**).

4.6 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.

4.7 Effects on Ability to Drive and Use Machines

None known.

4.8 Undesirable Effects

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:

	Frequency in percent of subjects	
	Gemfibrozil (N=2046)	Placebo (N=2035)
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:

	Frequency in percent of subjects	
	Gemfibrozil (N=2046)	Placebo (N=2035)
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

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, rhabdomyolysis
Skin and subcutaneous tissue disorders	Exfoliative dermatitis, rash, dermatitis, pruritus, angioedema, urticaria
Respiratory, thoracic and mediastinal disorders	Laryngeal edema
Blood and lymphatic system disorders	Severe anemia, leukopenia, thrombocytopenia, eosinophilia, bone marrow hypoplasia (see section **4.4 Special Warnings and Precautions for Use – Hematopoietic**)

Additional adverse reactions that have been reported included photosensitivity, alopecia, cholecystitis and cholelithiasis (see section **4.4 Special Warnings and Precautions for Use**).

4.9 Overdose

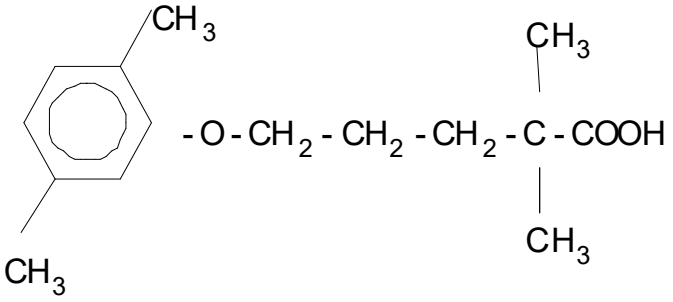
Overdosage has been reported with gemfibrozil. Symptoms reported with overdosage were abdominal cramps, abnormal LFTs, diarrhea, increased creatine phosphokinase (CPK), joint and muscle pain, nausea and vomiting. The patients fully recovered.

Symptomatic supportive measures should be taken should overdosage occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 58ºC to 61°C. Its solubility is 0.0019% in water and acid and over 1% in dilute base. Gemfibrozil is stable under ordinary conditions.

Mechanism of Action

Gemfibrozil's mechanism of action has not been definitively established. In humans, gemfibrozil inhibits peripheral lipolysis and decreases the hepatic extraction of free fatty acids. Gemfibrozil also inhibits synthesis and increases clearance of apolipoprotein B, which is a carrier of very-low-density lipoprotein (VLDL), leading to a decrease in VLDL production. Gemfibrozil increases the level of high-density lipoprotein (HDL) subfractions, HDL2 and HDL3 as well as apolipoprotein A-I and A-II. Animal studies suggest that the turnover and removal of cholesterol from the liver is increased by gemfibrozil.

Gemfibrozil is a lipid-regulating agent which reduces total cholesterol, low-density lipoprotein (LDL) cholesterol, VLDL and triglycerides and increases HDL cholesterol.

In the Helsinki Heart Study, a large, randomized, double-blind, placebo-controlled primary prevention trial, involving subjects with serum non-HDL cholesterol over 200 mg/dL (5.2 mmol/L) and no previous history of heart disease, gemfibrozil produced a significant reduction in total plasma triglycerides, moderate reductions in total and LDL cholesterol and a significant increase in HDL cholesterol. Over the 5-year study period, the gemfibrozil group experienced a 34% reduction in the overall incidence of CHD (in Years 4 and 5 of the study, the reduction in CHD was greater than 50%). There was a 37% reduction in

non-fatal MI and a 26% reduction in cardiac deaths. The overall difference in the incidence of CHD was significantly lower for gemfibrozil-treated patients than for those receiving placebo ($p<0.02$, two-tailed).

5.2 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 hours before meals. Average AUC was reduced by 14% to 44% when gemfibrozil was administered after meals compared to 0.5 hours before meals. In a subsequent study, the 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 **4.2 Posology and Method of Administration**).

Distribution

Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other drugs (see section **4.4 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.

5.3 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.

Long-term studies have been conducted in mice at 0.1 and 0.7 times the human exposure (based on AUC). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates. Administration of approximately two times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about 8 weeks and it was not transmitted to the offspring. Minor fetotoxicity was manifested by reduced birth weights observed at the high-dose levels.

6 PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

Not relevant.

6.2 Shelf Life

Please see detail on carton.

6.3 Special Precautions for Storage

Please see detail on carton.

Lopid (300 mg), Lopid (600 mg):

Manufactured by: OLIC (Thailand) Limited.

For: Pfizer (Thailand) Limited

Lopid O.D. (900 mg):

Marketing Authorization Holder: Pfizer (Thailand) Limited

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