SCHEDULING STATUS: **S3**

PROPRIETARY NAME AND DOSAGE FORM:

LOPID® 600 tablet

COMPOSITION:

Each tablet contains 600 mg gemfibrozil.

LOPID tablets contain the following inactive ingredients: microcrystalline cellulose, pregelatinised starch, colloidal anhydrous silica, polysorbate 80, sodium starch glycollate, magnesium stearate, methyl hydroxypropyl cellulose, titanium dioxide, talc, polydimethyl siloxane and polyethylene glycol 6000.
Sugar free.

CATEGORY AND CLASS:

A 7.5 Serum-cholesterol reducers

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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

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.

Pharmacokinetic properties:

Absorption:

Gemfibrozil is well absorbed after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1½ hours following multiple doses. Plasma levels appear proportional to the dose and do not demonstrate accumulation with 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 medicine were significantly increased when administered ½ an hour before meals. Average AUC was reduced by 14 – 44 % when gemfibrozil was administered after meals compared to ½ an hour before meals. In a subsequent study, rate of absorption of gemfibrozil was maximum when administered ½ an hour before meals with the C_{max} 50 – 60 % greater than when either with meals or fasting. In this study, there were no significant effects on AUC of timing of dose relative to meals (see DOSAGE AND DIRECTIONS FOR USE).

Distribution:

Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other medicines (see INTERACTIONS).

Metabolism:

Gemfibrozil undergoes oxidation of a ring methyl group to successively form 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 faeces.

INDICATIONS:

LOPID is indicated as adjunctive therapy to diet and weight loss in the treatment of the following hyperlipidaemias:

- Fredrickson type IIb (mixed hyperlipidaemia)
- Fredrickson type IV.

Note: LOPID should be prescribed only for patients with a potentially responsive lipid or lipoprotein abnormality where appropriate dietary therapy alone is insufficient to correct the condition.

The potential benefit of LOPID in treating type IIa patients with elevation of LDL-only is not likely to outweigh the risks.

LOPID therapy may be considered in those type IIb patients who have low HDL levels in addition to elevated LDL and triglyceride levels and who have had inadequate response to non-medicine therapy, or other medicines such as bile acid sequestrants or nicotinic acid.

Excess body weight and excessive alcohol intake may be important factors in hypertriglyceridaemia and should be addressed prior to any medicine therapy. Appropriate physical exercise may be a valuable ancillary measure. Contributory underlying pathology should be adequately treated e.g. hypothyroidism and diabetes mellitus.

CONTRAINDICATIONS:

LOPID is contraindicated in patients with:

- Hypersensitivity to gemfibrozil or any of the excipients
- Hepatic and/or severe renal dysfunction, including primary biliary cirrhosis
- Pre-existing gallbladder disease.

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

- simvastatin
- repaglinide
- dasabuvir (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS)
- selexipag.

WARNINGS AND SPECIAL PRECAUTIONS:

Cholelithiasis:

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

HMG-CoA reductase inhibitors:

The concomitant administration of LOPID with simvastatin is contraindicated (see CONTRAINDICATIONS). There have been reports of severe myositis with markedly elevated creatine kinase and myoglobinuria (rhabdomyolysis) when LOPID and the HMG-CoA reductase inhibitors, were used concomitantly. In most subjects who have had an unsatisfactory lipid response to either medicine alone, the possible benefit of combined therapy with a HMG-CoA reductase inhibitor and LOPID does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (see CONTRAINDICATIONS and INTERACTIONS).

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 stabilised.

CYP2C8 substrates:

LOPID, an inhibitor of CYP2C8, may increase exposure of CYP2C8 substrates when administered concomitantly (see CONTRAINDICATIONS and INTERACTIONS).

Laboratory tests:

Elevated liver function tests have been observed during LOPID administration, including elevations of AST (SGOT), ALT (SGPT), LDH and alkaline phosphatase. Increased CK and bilirubin have rarely been reported with LOPID administration. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

Haematopoietic:

Mild haemoglobin, haematocrit and white blood cell decreases have been observed following initiation of LOPID therapy. However, these levels stabilise during long-term administration. Less frequently, severe anaemia, leukopenia, thrombocytopenia, eosinophilia and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

Diabetes mellitus:

As LOPID may elevate the fasting blood sugars during treatment, periodic blood sugar determinations are advisable in diabetics receiving LOPID to assure adequate control.

General:

Because long-term administration of LOPID may be needed, all baseline values including lipid profile, blood count and liver function tests, should be reliably measured before treatment and periodic determinations of serum lipids should be obtained. LOPID should be withdrawn after 3 months if the response is inadequate. A paradoxical elevation of serum lipids has occasionally been observed, usually in patients with alcoholic hepatic disease.

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

Effects on ability to drive and use machines:

In rare cases, LOPID causes dizziness and affects your eyesight which may affect your ability to drive or operate machinery.

INTERACTIONS:

Anticoagulants:

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

HMG-CoA reductase inhibitors:

The concomitant administration of LOPID with simvastatin is contraindicated. There have been reports of severe myositis with markedly elevated creatine kinase and myoglobinuria (rhabdomyolysis) when LOPID and the HMG-CoA reductase inhibitors were used concomitantly (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

CYP2C8 substrates:

LOPID is an inhibitor of CYP2C8 and may increase exposure of medicines mainly metabolised by CYP2C8 (e.g., dabrafenib, enzalutamide, loperamide, montelukast, paclitaxel, pioglitazone, rosiglitazone) (see WARNINGS AND SPECIAL PRECAUTIONS). Therefore, dosing reduction of medicines that are mainly metabolised by CYP2C8 enzyme may be required when LOPID is used concomitantly.

In healthy volunteers, co-administration with LOPID significantly increased AUC and C_{max} of repaglinide by 8,1 fold and 2,4 fold respectively. In the same study, co-administration with LOPID and itraconazole increased the AUC and C_{max} of repaglinide by 19,4 fold and 2,8 fold respectively. In addition, co-administration with LOPID or with LOPID and intraconazole prolonged its hypoglycaemic effects. Co-administration of LOPID and repaglinide increases the risk for severe hypoglycaemia and is contraindicated (see CONTRAINDICATIONS).

Co-administration of LOPID 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 LOPID with dasabuvir is contraindicated (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

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

In healthy volunteers given a single 160 mg dose of enzalutamide after LOPID 600 mg twice daily, the AUC of enzalutamide plus active metabolite (N-desmethyl enzalutamide) 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 WARNINGS AND SPECIAL PRECAUTIONS).

Bile acid-binding resins:

Reduced bioavailability of LOPID may result when given simultaneously with resin-granule medicines such as colestipol. Administration of the medicines two hours or more apart is recommended.

Colchicine:

Risk of neuromuscular toxicity and rhabdomyolysis may be increased with concomitant administration of colchicine and LOPID. 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 LOPID is an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, organic anion-transporting polypeptide (OATP) 1B1 and UDP-glucuronosyltransferase (UGT) 1A1 and 1A3 (see WARNINGS AND SPECIAL PRECAUTIONS).

HUMAN REPRODUCTION:

Safe use in pregnancy has not been established. It is not known whether or not LOPID is secreted in human milk. LOPID should be avoided during pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE:

1 200 mg daily in two divided doses 30 minutes before the morning and evening meals, is the usual dose.

900 mg daily in two divided doses will prove sufficient in some patients and should be tried in cases of intolerance at normal dosage.

When maximal triglyceride reduction is desired up to 1 500 mg daily in divided doses may be needed.

LOPID should be withdrawn after 3 months if the response is inadequate.

Use in children:

Safety and efficacy in children have not been established.

SIDE EFFECTS:

Side effects reported in clinical trials were categorised utilising the incidence rate as follows:

Very common: ≥ 1/10 (≥ 10 %)

Common: ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %)

Uncommon: ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %)

Rare: ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %)

Adverse event frequency

(% of patients)

Adverse event	**LOPID** **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

Adverse event	**LOPID** **N = 2046**	**Placebo** **N = 2035**
Diarrhoea	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 LOPID is probable are:

MedDRA system organ class	**Adverse reaction**
Blood and lymphatic system disorders	Severe anaemia, leukopenia, thrombocytopenia, eosinophilia, bone marrow hypoplasia
Psychiatric disorders	Decreased libido, depression
Nervous system disorders	Dizziness, somnolence, paraesthesia, peripheral neuritis, headache
Eye disorders	Blurred vision
Respiratory, thoracic and mediastinal disorders	Laryngeal oedema
Gastrointestinal disorders	Pancreatitis
Hepatobiliary disorders	Cholestatic jaundice
Skin and subcutaneous tissue disorders	Exfoliative dermatitis, rash, dermatitis, pruritus, angioedema, urticaria
Musculoskeletal and connective tissue disorders	Arthralgia, synovitis, myalgia, myopathy, myasthenia, painful extremities, rhabdomyolysis
Reproductive system and breast disorders	Impotence

Additional adverse reactions that have been reported include the following:

Photosensitivity, alopecia, cholecystitis and cholelithiasis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms reported with overdosage were abdominal cramps, abnormal LFTs, diarrhoea, increased CPK, joint and muscle pain, nausea and vomiting.

Symptomatic supportive measures should be taken should overdosage occur.

IDENTIFICATION:

White, film-coated, oval, biconvex tablet.

PRESENTATION:

Tablets in blisters of 60.

STORAGE INSTRUCTIONS:

Store at or below 25 ºC in a cool, dry place.

Keep out of reach of children.

REGISTRATION NUMBER:

Y/7.5/245

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

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