Lopid®

Gemfibrozil

600 mg Film coated tablets

Reference Market: Germany

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

- Lopid 600 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg gemfibrozil.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

film-coated tablet

Description

- Lopid 600 mg: white, biconvex, oval, film-coated tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Lopid is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:
- Treatment of severe hypertriglyceridaemia with or without low HDL cholesterol.
- Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.
- Primary hypercholesterolaemia when a statin is contraindicated or not tolerated.

Primary prevention
Reduction of cardiovascular morbidity in males with increased non-HDL cholesterol and at high risk for a first cardiovascular event when a statin is contraindicated or not tolerated (see section 5.1).

4.2. Posology and method of administration

Prior to initiating gemfibrozil, other medical problems such as hypothyroidism and diabetes mellitus must be controlled as best as possible and patients should be placed on a standard lipid-lowering diet, which should be continued during treatment. Lopid should be taken orally.

Posology

Adult
The dose range is 900 mg to 1200 mg daily.
The only dose with documented effect on morbidity is 1200 mg daily.

See Method of administration.

Elderly (over 65 years old)
As for adults

Children and adolescents
Gemfibrozil therapy has not been investigated in children. Due to the lack of data the use of Lopid in children is not recommended.

Renal impairment

In patients with mild to moderate renal impairment (Glomerular filtration rate 50 - 80 and 30 - < 50 ml/min/1.73 m^2, respectively), start treatment at 900 mg daily and assess renal function before increasing dose. Lopid should not be used in patients with severely impaired renal function (see section 4.3).

Hepatic impairment
Gemfibrozil is contraindicated in hepatic impairment (see section 4.3).

Method of administration
The 1200 mg dose is taken as 600 mg twice daily, half an hour before breakfast and half an hour before the evening meal.

The 900 mg dose is taken as a single dose half an hour before the evening meal.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hepatic impairment
- Severe renal impairment
- History of/or pre-existing gall bladder or biliary tract disease, including gallstones
- Concomitant use of repaglinide, dasabuvir, selexipag (see section 4.5), simvastatin, or rosuvastatin at 40 mg (see sections 4.4 and 4.5)
- Patients with previous history of photoallergy or phototoxic reaction during treatment with fibrates

4.4. Special warnings and special precautions for use

Muscle disorders (myopathy/rhabdomyolysis)
There have been reports of myositis, myopathy and markedly elevated creatine phosphokinase associated with gemfibrozil. Rhabdomyolysis has also been reported rarely.

Muscle damage must be considered in any patient presenting with diffuse myalgia, muscle tenderness and/or marked increase in muscle CPK levels (>5x ULN); under these conditions treatment must be discontinued.

Concomitant 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 and myoglobinuria (rhabdomyolysis) when gemfibrozil and HMG CoA reductase inhibitors were used concomitantly (see sections 4.3 and 4.5). Pharmacokinetic interactions may also be present (see also section 4.5) and dosage adjustments may be necessary.

The benefit of further alterations in lipid levels by the combined use of gemfibrozil and HMG-CoA reductase inhibitors should be carefully weighed against the potential risks of such combinations and clinical monitoring is recommended.

A creatine phosphokinase (CPK) level should be measured before starting such a combination in patients with pre-disposing factors for rhabdomyolysis as follows:
- renal impairment
- hypothyroidism
- alcohol abuse
- age > 70 years
- personal or family history of hereditary muscular disorders

- previous history of muscular toxicity with another fibrate or HMG-CoA reductase inhibitor

In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with HMG-CoA reductase inhibitors and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis and acute renal failure.

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

Monitoring serum lipids
Periodic determinations of serum lipids are necessary during treatment with gemfibrozil. Sometimes a paradoxical increase of (total and LDL) cholesterol can occur in patients with hypertriglyceridaemia. If the response is insufficient after 3 months of therapy at recommended doses treatment should be discontinued and alternative treatment methods considered.

Monitoring liver function
Elevated levels of ALAT, ASAT, alkaline phosphatase, LDH, CK and bilirubin have been reported. These are usually reversible when gemfibrozil is discontinued. Therefore liver function tests should be performed periodically. Gemfibrozil therapy should be terminated if abnormalities persist.

Monitoring blood counts
Periodic blood count determinations are recommended during the first 12 months of gemfibrozil administration. Anaemia, leucopenia, thrombocytopenia, eosinophilia and bone marrow hypoplasia have been reported rarely (see section 4.8).

Interactions with other medicinal products (see also sections 4.3 and 4.5)
Concomitant use with CYP2C8, CYP2C9, CYP2C19, CYP1A2, UGTA1, UGTA3 and OATP1B1 substrates
The interaction profile of gemfibrozil is complex resulting in increased exposure of many medicinal products if administered concomitantly with gemfibrozil.

Gemfibrozil potently inhibits CYP2C8, CYP2C9, CYP2C19, CYP1A2 and UDP glucuronyltransferase (UGTA1 and UGTA3) enzymes and also inhibits organic anion-transporting polypeptide 1B1 (OATP1B1) (see section 4.5). In addition, gemfibrozil is metabolised to gemfibrozil 1-O-β-glucuronide which also inhibits CYP2C8 and OATP1B1.

Concomitant use with hypoglycaemic agents
There have been reports of hypoglycaemic reactions after concomitant use with gemfibrozil and hypoglycaemic agents (oral agents and insulin). Monitoring of glucose levels is recommended.

Concomitant anticoagulants
Gemfibrozil may potentiate the effects of coumarin type vitamin K antagonist anticoagulants such as warfarin, acenocoumarol, or phenprocoumon. The concomitant administration of gemfibrozil with these anticoagulants necessitates careful monitoring of prothrombin time (INR - International Normalised Ratio). Caution should be exercised when such a coumarin type vitamin K antagonist anticoagulant is given concomitantly with gemfibrozil. The dosage of the anticoagulant may need to be reduced to maintain desired prothrombin time levels (see section 4.5).

Dietary sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets should be informed that this medicinal product is essentially ‘sodium-free’.

4.5. Interaction with other medicinal products and other forms of interaction

The interaction profile of gemfibrozil is complex. In vivo studies indicate that gemfibrozil and its metabolite gemfibrozil 1-O-β-glucuronide are potent inhibitors of CYP2C8 (an enzyme important for the metabolism of e.g. dabrafenib, enzalutamide, loperamide, montelukast, repaglinide, rosiglitazone, pioglitazone, dasabuvir, selexipag and paclitaxel). Co-administration of gemfibrozil with repaglinide, dasabuvir or selexipag is contraindicated (see section 4.3). In addition, dosing reduction of drugs that are mainly metabolised by CYP2C8 enzyme may be required when gemfibrozil is used concomitantly. In vitro studies have shown that gemfibrozil is a strong inhibitor of CYP2C9 (an enzyme involved in the metabolism of e.g. warfarin and glimepiride), but also of CYP 2C19, CYP1A2, OATP1B1 and UGTA1 and UGTA3 (see section 4.4). Gemfibrozil 1-O-β-glucuronide also inhibits OATP1B1.

Repaglinide
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 hypoglycaemic effects. Therefore, co-administration of gemfibrozil and repaglinide increases the risk for severe hypoglycaemia and is contraindicated (see section 4.3).

Dasabuvir
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 section 4.3).

Selexipag
Co-administration of gemfibrozil with selexipag, a substrate for CYP2C8, 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).

Enzalutamide
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-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. Concomitant treatment of gemfibrozil and enzalutamide should be avoided; if co-administration is considered necessary, the dose of enzalutamide should be reduced (see section 4.4).

Rosiglitazone
The combination of gemfibrozil with rosiglitazone should be approached with caution. Co-administration with rosiglitazone has resulted in 2.3-fold increase in rosiglitazone systemic exposure, probably by inhibition of the CYP2C8 isozyme (see section 4.4).

HMG CoA reductase inhibitors
The concomitant administration of gemfibrozil with simvastatin, as well as with rosuvastatin at 40 mg is contraindicated (see sections 4.3 and 4.4). The combined use of gemfibrozil and a statin should generally be avoided (see section 4.4). The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse events, including rhabdomyolysis, has been reported when fibrates are co-administered with statins.

Gemfibrozil has also been reported to influence the pharmacokinetics of simvastatin, lovastatin, pravastatin, rosuvastatin and atorvastatin. Gemfibrozil caused an almost 3-fold increased in AUC of

simvastatin acid possibly due to inhibition of glucoronidation via UGTA1 and UGTA3, and a 3-fold increase in pravastatin AUC which may be due to interference with transport proteins. One study indicated that the co-administration of a single rosuvastatin dose of 80 mg to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in a 2.2-fold increase in mean C_{max} and a 1.9-fold increase in mean AUC of rosuvastatin. The co-administration of a single lovastatin dose of 40 mg with gemfibrozil (600 mg twice daily for 3 days) in healthy volunteers resulted in a 2.8-fold increase of the mean AUC and C_{max} of lovastatin acid. The co-administration of a single atorvastatin dose of 40 mg with gemfibrozil (600 mg twice daily for 7 days) in healthy volunteers resulted in a 1.35-fold increase in mean AUC and no increase in mean C_{max} of atorvastatin.

Anticoagulants
Gemfibrozil may potentiate the effects of coumarin type vitamin K antagonist anticoagulants such as warfarin, acenocoumarol, or phenprocoumon. The concomitant administration of gemfibrozil with these anticoagulants necessitates careful monitoring of prothrombin time (INR) (see section 4.4).

Bexarotene
Concomitant administration of gemfibrozil with bexarotene is not recommended. A population analysis of plasma bexarotene concentrations in patients with cutaneous T-cell lymphoma (CTCL) indicated that concomitant administration of gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene.

Bile acid – binding resins
Reduced bioavailability of gemfibrozil may result when given simultaneously with resin-granule drugs such as colestipol. Administration of the products two hours or more apart is recommended.

Colchicine
Risk of myopathy 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. Clinical and biological monitoring are recommended, especially at the start of combined treatment.

Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other drugs.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on use of Lopid in pregnant women. Animal studies are insufficiently clear to allow conclusions to be drawn on pregnancy and foetal development (see section 5.3). The potential risk for humans is unknown. Lopid should not be used during pregnancy unless it is clearly necessary.

Breast-feeding
There are no data on excretion of gemfibrozil in milk. Lopid should not be used when breast-feeding.

Fertility
Reversible decreases in male fertility have been observed in reproductive toxicity studies in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. In isolated cases dizziness and visual disturbances can occur which may negatively influence driving.

4.8 Undesirable effects

Most commonly reported adverse reactions are of gastrointestinal character and are seen in approximately 7% of the patients. These adverse reactions do not usually lead to discontinuation of the treatment.

Adverse reactions are ranked according to frequency using the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), including isolated reports:

System Organ Class	Undesirable effect
Blood and lymphatic system disorders Rare	Bone marrow failure, severe anaemia, thrombocytopenia, leukopenia, eosinophilia
Psychiatric disorders Rare	Depression, decreased libido
Nervous system disorders Common Rare	Vertigo, headache Neuropathy peripheral, paraesthesia, dizziness, somnolence
Eye disorders Rare	Vision blurred
Cardiac disorders Uncommon	Atrial fibrillation
Respiratory, thoracic and mediastinal disorders Rare	Laryngeal oedema
Gastrointestinal disorders Very common Common Rare	Dyspepsia Diarrhoea, vomiting, nausea, abdominal pain constipation, flatulence Pancreatitis, appendicitis
Hepatobiliary disorders Rare	Jaundice cholestatic, hepatitis, cholelithiasis, cholecystitis, hepatic function abnormal
Skin and subcutaneous tissue disorders Common Rare	Eczema, rash Angioedema, dermatitis exfoliative, urticaria, dermatitis, alopecia, photosensitivity reaction, pruritus
Musculoskeletal and connective tissue disorders Rare	Rhabdomyolysis, myopathy, myositis, muscular weakness, synovitis, myalgia, arthralgia, pain in extremity
Reproductive system and breast disorder Rare	Erectile dysfunction
General disorders and administration site conditions Common	Fatigue
Investigations	

System Organ Class	Undesirable effect
Rare	Haemoglobin decreased, haematocrit decreased, white blood cell count decreased, blood creatine phosphokinase increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

4.9 Overdose

Overdose has been reported. Symptoms reported with overdosage were abdominal cramps, abnormal LFT's, diarrhea, increased CPK, joint and muscle pain, nausea and vomiting. The patients fully recovered. Symptomatic supportive measures should be taken if overdose occurs.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Serum-lipid lowering agent
Chemical subgroup: Fibrates
ATC code: C10A B04

Gemfibrozil is a non-halogenated phenoxypentanoic acid. Gemfibrozil is a lipid regulating agent which regulates lipid fractions.

Gemfibrozil's mechanism of action has not been definitively established. In man, gemfibrozil stimulates the peripheral lipolysis of triglyceride rich lipoproteins such as VLDL and cholymicrons (by stimulation of LPL). Gemfibrozil also inhibits synthesis of VLDL in the liver. Gemfibrozil increases the HDL_2 and HDL_3 subfractions 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.

There is evidence that treatment with fibrates may reduce coronary heart disease events but they have not been shown to decrease all cause mortality in the primary or secondary prevention of cardiovascular disease.

In the Helsinki Heart Study, which was a large placebo-controlled study with 4081 male subjects, 40 to 55 years of age, with primary dyslipidaemia (predominantly raised non-HDL cholesterol +/- hypertriglyceridaemia), but no previous history of coronary heart disease, gemfibrozil 600 mg twice daily, produced a significant reduction in total plasma triglycerides, total and low density lipoprotein cholesterol and a significant increase in high density lipoprotein cholesterol. The cumulative rate of cardiac end-points (cardiac death and non-fatal myocardial infarction) during a 5 year follow-up was 27.3/1,000 in the gemfibrozil group (56 subjects) and 41.4/1000 in the placebo group (84 subjects) showing a relative risk reduction of 34.0% (95% confidence interval 8.2 to 52.6, $p<0.02$) and an absolute risk reduction of 1.4% in the gemfibrozil group compared to placebo. There was a 37% reduction in non-fatal myocardial infarction and a 26% reduction in cardiac deaths. The number of deaths from all causes was, however, not different (44 in the gemfibrozil group and 43 in the placebo group). Diabetes patients and patients with severe lipid fraction deviations showed a 68% and 71% reduction of CHD endpoints, respectively.

The VA-HIT study was a double-blind study comparing gemfibrozil (1200 mg per day) with placebo in 2531 men with a history of coronary heart disease, HDL-C levels of < 40 mg/dL (1.0 mmol/L), and normal LDL C levels. After one year, the mean HDL-C level was 6% higher and the mean triglyceride level was 31% lower in the gemfibrozil group than in the placebo group. The primary event of non-fatal myocardial infarction or cardiac death occurred in 17.3% of gemfibrozil-treated and 21.7% of placebo-treated patients (reduction in relative risk 22%; 95% CI, 7 to 35 %; P=0.006). Among secondary outcomes, patients treated with gemfibrozil experienced relative risk reductions of 25% (95% CI–6-47%, p=0.10) for stroke, 24% (95% CI 11-36%, p< 0.001) for the combined outcome of death from CHD, non-fatal myocardial infarction, or confirmed stroke, 59% (95% CI 33-75%, p<0.001) for transient ischaemic attack, and 65% (95% CI 37-80%, p< 0.001) for carotid endarterectomy.

5.2. Pharmacokinetic properties

Absorption
Gemfibrozil is well absorbed from the gastro-intestinal tract after oral administration with a bioavailability close to 100%. As the presence of food alters the bioavailability slightly gemfibrozil should be taken 30 minutes before a meal. Peak plasma levels occur in one to two hours. After administration of 600 mg twice daily a C_{max} in the range 15 to 25 mg/L is obtained.

Distribution
Volume of distribution at steady state is 9-13 L. The plasma protein binding of gemfibrozil and its main metabolite are at least 97%.

Biotransformation
Gemfibrozil undergoes oxidation of a ring methyl group to form successively a hydroxymethyl and a carboxyl metabolite (the main metabolite). This metabolite has a low activity compared to the mother compound gemfibrozil and an elimination half-life of approximately 20 hours. Glucuronidation to gemfibrozil 1-O-β-glucuronide is another important elimination pathway for gemfibrozil in man.

The enzymes involved in the metabolism of gemfibrozil are not known. The interaction profile of gemfibrozil and its metabolites is complex (see sections 4.3, 4.4 and 4.5). In vitro and in vivo studies have shown that gemfibrozil inhibits CYP2C8, CYP2C9, CYP2C19, CYP1A2, UGTA1, UGTA3 and OATP1B1. Gemfibrozil 1-O-β-glucuronide also inhibits CYP2C8 and OATP1B1.

Elimination
Gemfibrozil is eliminated mainly by metabolism. Approximately 70% of the administered human dose is excreted in the urine, mainly as conjugates of gemfibrozil and its metabolites. Less than 6% of the dose is excreted unchanged in the urine. Six percent of the dose is found in faeces. The total clearance of gemfibrozil is in the range 100 to 160 ml/min, and the elimination half-life is in the range 1.3 to 1.5 hours. The pharmacokinetics is linear within the therapeutic dose range.

Special patient groups
No pharmacokinetic studies have been performed in patients with impaired hepatic function.
There are limited data on patients with mild, moderate and non-dialysed severe renal impairment. The limited data support the use of up to 1200 mg a day in patients with mild to moderate renal failure not receiving another lipid lowering drug.

5.3 Preclinical safety data

In a 2-year study of gemfibrozil, subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3%, of male rats treated at 10 times the human dose.

In a mouse carcinogenicity study at dosages corresponding to 0.1 and 0.7 times the clinical exposure (based on AUC), there were no significant differences from controls in the incidence of tumours. In a rat carcinogenicity study at dosages corresponding to 0.2 and 1.3 times the clinical exposure (based on AUC), the incidence of benign liver nodules and liver carcinomas was significantly increased in high dose males, and the incidence of liver carcinomas increased also in the low dose males, but this increase was not statistically significant.

Liver tumours induced by gemfibrozil and other fibrates in small rodents are generally considered to be related to the extensive proliferation of peroxisomes in these species and, consequently, of minor clinical relevance.

In the male rat, gemfibrozil also induced benign Leydig cell tumours. The clinical relevance of this finding is minimal.

In reproductive toxicity studies, administration of gemfibrozil at approximately 2 times the human dose (based on body surface area) to male rats for 10 weeks resulted in decreased fertility. Fertility was restored after a drug-free period of 8 weeks. Gemfibrozil was not teratogenic in either rats or rabbits. Administration of 1 and 3 times the human dose (based on body surface area) of gemfibrozil to female rabbits during organogenesis caused a dose-related decrease in litter size. Administration of 0.6 and 2 times the human dose (based on body surface area) of gemfibrozil to female rats from gestation Day 15 through weaning caused dose-related decreases in birth weight and suppression of pup growth during lactation. Maternal toxicity was observed in both species and the clinical relevance of decreases in rabbit litter size and rat pup weight is uncertain.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet excipients:
Magnesium stearate
Microcrystalline Cellulose
Pregelatinized starch
Colloidal silica (anhydrous) (E551)
Polysorbate 80 (E433)
Sodium starch gylcollate

Tablet coating:
Hydroxypropylmethylcellulose (E464)
Titanium dioxide E171
Talc (E553b)
Polydimethyl siloxane
Polyethylene glycol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use Lopid after the expiry date which is stated on the carton / Blister after EXP:. The expiry date refers to the last day of that month.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

PVC/Auminium blisters with 14, 20, 28, 30, 50, 56, 60, 98, 100, 196, 500 and 600 tablets.

Not all pack sizes maybe marketed.

6.6 Special precautions for disposal and other handling

Keep out of the sight and reach of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

MARKETING AUTHORIZATION HOLDER
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THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists