AUSTRALIAN PRODUCT INFORMATION

LIPIGEM®

(gemfibrozil) tablets

1 NAME OF THE MEDICINE

Gemfibrozil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LIPIGEM tablet contains 600 mg of gemfibrozil as the active ingredient.

Excipient with known effects: lactose and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

LIPIGEM: 19 mm x 9.2 mm deep convex, white, film coated oval shape tablet, debossed "GL600" on one side and Greek alpha on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LIPIGEM is indicated as an adjunct to diet and other therapeutic measures for:

- Severe hypertriglyceridaemia (Type IV and V) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them.
- Dyslipidaemia associated with diabetes.
- Reduction of risk of coronary heart disease in patients with Type IIa and IIb hypercholesterolaemia.

Because of potential toxicity such as malignancy, gallbladder disease, abdominal pain leading to appendectomy and other abdominal surgeries, an increased incidence in noncoronary mortality, and the 29% increase in all-cause mortality seen with the chemically and pharmacologically related drug, clofibrate, the potential benefits of gemfibrozil in treating Type IIa patients with elevations of LDL-cholesterol only is not likely to outweigh the risks. In a subgroup analysis of patients in the Helsinki Heart Study with above-median HDL-cholesterol values at baseline (greater than 1.2 mmol/L), the incidence of serious coronary events was similar for gemfibrozil and placebo subgroups.

NOTE: LIPIGEM IS INDICATED WHEN EXERCISE, WEIGHT LOSS AND SPECIFIC DIETARY OR OTHER NONDRUG MEASURES SUCH AS LIMITING ALCOHOL INTAKE HAVE FAILED. OTHER MEDICAL DISORDERS SUCH AS HYPOTHYROIDISM AND DIABETES SHOULD BE CONTROLLED AS MUCH AS POSSIBLE.

PERIODIC DETERMINATION OF SERUM LIPIDS SHOULD BE OBTAINED DURING TREATMENT WITH LIPIGEM THE DRUG SHOULD BE WITHDRAWN OR ADDITIONAL THERAPY INSTITUTED IF THE LIPID RESPONSE IS DEEMED INADEQUATE AFTER THREE MONTHS.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose for adults is 600 mg twice daily (total daily dose 1200 mg) administered one half hour before the morning and evening meal.

For patients who cannot tolerate LIPIGEM when given half an hour before food, LIPIGEM may be taken with food. The bioavailability of gemfibrozil is higher when administered half an hour before food.

Use in Patients with Hepatic Dysfunction

LIPIGEM is contraindicated in patients with hepatic dysfunction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.3 CONTRAINDICATIONS).

Use in Patients with Renal Dysfunction

LIPIGEM is contraindicated in patients with severe renal dysfunction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.3 CONTRAINDICATIONS).

4.3 CONTRAINDICATIONS

LIPIGEM is contraindicated in

- Hypersensitivity to gemfibrozil or any of the excipients in the formulation
- Hepatic dysfunction including primary biliary cirrhosis
- Severe renal dysfunction
- Pregnant or lactating women
- Pre-existing gallbladder or biliary tract disease including gallstones (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- Patients with previous history of photoallergy or phototoxic reaction during treatment with fibrates
- Type I hyperlipoproteinaemia
- Concomitant use with any of the following:
    - simvastatin
    - repaglinide
    - dasabuvir

(See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Because of chemical, pharmacological and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organisation (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the one and a half years follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the gemfibrozil group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the gemfibrozil group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the gemfibrozil group (43 versus 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the one and a half years since the trial was completed was 39 in the gemfibrozil group and 29 in the placebo group

(difference not statistically significant). This includes 5 basal cell carcinomas in the gemfibrozil group and none in the placebo group (p=0.06); historical data predicted an expected 4.7 cases in the placebo group. Gastrointestinal malignancies and deaths from malignancies were not statistically different between gemfibrozil and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward greater prevalence of gallstones during the study within the gemfibrozil treatment group (7.5% versus 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the gemfibrozil group (17 versus 11 subjects, a 54% excess).

This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. LIPIGEM therapy should be discontinued if gallstones are found.

Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumours were increased in rats, gemfibrozil should be administered only to those patients described in Section 4.1 THERAPEUTIC INDICATIONS. If a significant serum response is not obtained, LIPIGEM should be discontinued.

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.

A creatine phosphokinase (CPK) level should be measured before starting such a treatment 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.

Concomitant Anticoagulants

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

Concomitant 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 and myoglobinuria (rhabdomyolysis) when gemfibrozil and HMG-CoA reductase inhibitors were used concomitantly. 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 Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). The use of fibrates alone, including gemfibrozil, may occasionally be associated with myositis. Patients receiving gemfibrozil and complaining of muscle pain, tenderness or weakness should have prompt medical evaluation for myositis, including serum

creatine kinase level determination. If myositis is suspected or diagnosed, gemfibrozil therapy should be withdrawn.

Concomitant CYP2C8 Substrates

Gemfibrozil, an inhibitor of CYP2C8, may increase exposure of CYP2C8 substrates when administered concomitantly (see Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Cataracts

Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

Use in Patients with Cholelithiasis

Gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. However, in the Helsinki Heart Study, gemfibrozil did not significantly increase the need for cholecystectomy compared to placebo. If cholelithiasis is suspected, gallbladder studies are indicated. Gemfibrozil therapy should be discontinued if gallstones are found.

Monitoring Haematologic Changes

Mild haemoglobin, haemotocrit and white cell decreases have been observed occasionally on initiating gemfibrozil therapy. However, these levels stabilise during long-term administration. Rarely, severe anaemia, leukopaenia, thrombocytopaenia, eosinophilia and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of LIPIGEM administration.

Cardiac Arrhythmias

Although no clinically significant abnormalities occurred that could be attributed to gemfibrozil, the possibility exists that such abnormalities may occur.

Monitoring Serum Levels

Initial therapy.

Before instituting LIPIGEM therapy, attempts should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients and control of any causes of secondary hyperlipidaemia such as diabetes mellitus or hypothyroidism.

Long-term therapy.

Because long-term administration of LIPIGEM is recommended, pretreatment clinical chemistry studies should be performed to ensure that the patient has elevated serum lipid or low HDL cholesterol levels. Periodic determinations of serum lipids and lipoproteins should be done during LIPIGEM administration, including measurement of LDL-cholesterol/HDL-cholesterol ratio, particularly in Type IV hyperlipoproteinaemic patients.

Continued therapy.

Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

Peroxisome Proliferation

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following gemfibrozil administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans, but changes in peroxisome morphology have been observed.

Use in Hepatic Impairment

Hepatobiliary Disease

In patients with a past history of jaundice or hepatic disorder, LIPIGEM should be used with caution.

Use in the Elderly

No data available.

Paediatric Use

Safety and efficacy in children have not been established.

Effects on Laboratory Tests

Monitoring Liver Function

Abnormal liver function tests have been observed occasionally during gemfibrozil administration, including elevations of AST (SGOT), ALT (SGPT), LDH, alkaline phosphatase, creatine kinase (CK) and bilirubin. They are usually reversible when gemfibrozil is discontinued. Therefore, periodic liver function studies are recommended and LIPIGEM therapy should be terminated if abnormalities persist.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Anticoagulants

Caution should be exercised when anti-coagulants are given in conjunction with gemfibrozil. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has stabilised (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

CYP2C8 Substrates

Gemfibrozil is an inhibitor of CYP2C8 and may increase exposure of drugs mainly metabolised by CYP2C8 (e.g. dabrafebib, loperamide, montelukast, paclitaxel, pioglitazone, rosiglitazone). Therefore, dosing reduction of drugs that are mainly metabolised by CYP2C8 enzyme may be required when gemfibrozil is used concomitantly.

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.

Repaglinide

In healthy volunteers, co-administration of gemfibrozil with repaglinide increased the plasma concentration of repaglinide. The increase in the plasma concentration of repaglinide was more pronounced following the co-administration with the gemfibrozil-itraconazole combination. In addition, co-administration of gemfibrozil, or the gemfibrozil-itraconazole combination with repaglinide prolonged the hypoglycaemic effects of repaglinide. Therefore, co-administration of gemfibrozil and repaglinide increases the risk for severe hypoglycaemia and is contraindicated (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dasabuvir

Co-administration of gemfibrozil with dasabuvir increased the plasma concentration of dasabuvir 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 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

CYP enzymes, UGTA enzymes and OATP1B1 transporter

In-vitro studies have shown that gemfibrozil is an inhibitor of CYP2C8, CYP2C9, CYP2C19, CYP1A2, organic anion-transporting polypeptide (OATP) 1B1 and UDP-glucuronosyltransferase (UGT) 1A1 and 1A3. Therefore, caution should be exercised with concomitant use of gemfibrozil with CYP2C8, CYP2C9, CYP2C19, CYP1A2, OATP1B1, UGT1A1 and UGT1A3 substrates.

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.

HMG-CoA Reductase

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 were used concomitantly. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. 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. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The risk of serious toxicity is increased if gemfibrozil is used concomitantly with other fibrates. Such combination therapy should be used with caution only in patients with severe combined dyslipidaemia who have high cardiovascular risk and no history of muscular disease. Patients should be monitored closely for signs of muscle toxicity, although toxicity may occur even in the presence of such monitoring.

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 drugs two hours or more apart is recommended.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Administration of approximately 2 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 eight weeks and it was not transmitted to the offspring. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels.

Gemfibrozil was administered in oral doses of approximately 95 and 325 mg/kg/day to male and female rats for 61 and 15 days respectively before mating. Dosing was continued through pregnancy and weaning of

offspring. Gemfibrozil produced a dose-related suppression of fertility but had no effect on length of gestation, duration of parturition, litter size, or embryonic or fetal wastage. Treated males were responsible for the reduced fertility rate, probably because of the marked suppression of weight gain they experienced.

Use in Pregnancy

Pregnancy Category - B3

Reproduction studies have been performed in the rat at doses of 81 and 281 mg/kg/day and in the rabbit at 60 and 300 mg/kg/day. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to gemfibrozil. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that gemfibrozil is tumourigenic in male and female rats, the use of LIPIGEM in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

The physiological hyperlipidaemia of pregnancy does not require treatment.

Use in Lactation

The safe use of gemfibrozil in lactation has not been established. It is not known whether gemfibrozil and its metabolites are 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

No specific studies have been conducted to assess the direct effect of gemfibrozil on the ability to drive and use machines. However, adverse effects of gemfibrozil include dizziness and blurred vision which could affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (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:

Table 1. Adverse reactions in patients taking gemfibrozil and placebo

	Gemfibrozil (n=2046)	**Placebo (n=2035)**
	Frequency in % 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
(histologically confirmed in most cases where data were available)		
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects but without a significant difference between groups		
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

Gall bladder surgery was performed in 0.9% of gemfibrozil and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group in the WHO study.

Nervous system and special senses adverse reactions were more common in the gemfibrozil group. These included hypesthesia, paresthesia, and taste perversion. Other adverse reactions that were more common among the gemfibrozil treatment group subjects but where a causal relationship was not established included cataracts, peripheral vascular disease, and intracerebral haemorrhage.

From other studies it seems probable that gemfibrozil is causally related to the occurrence of musculoskeletal symptoms (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), and to abnormal liver function tests and haematologic changes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorised according to whether a causal relationship to treatment with gemfibrozil is probable or not established (see **Table 2**).

Table 2. Adverse reactions reported for gemfibrozil with probable or not established causal relationship

	CAUSAL RELATIONSHIP PROBABLE	**CAUSAL RELATIONSHIP NOT ESTABLISHED**
General disorders		weight loss
		extrasystoles
Hepatobiliary disorders	cholestatic jaundice	hepatoma
Gastrointestinal disorders	cholelithiasis	colitis
	pancreatitis	
Nervous System disorders	dizziness	confusion
	somnolence	convulsions
	paresthesia	syncope
	peripheral neuritis	
	headache	
Psychiatric disorders	decreased libido	
	depression	
Eye disorders	blurred vision	retinal oedema
Reproductive system and breast disorders	impotence	decreased male fertility
Genitourinary disorders		renal dysfunction
		renal failure as a consequence of rhabdomyolysis
Musculoskeletal and connective tissue disorders	myopathy	
	myasthenia	
	myalgia	
	painful extremities	
	arthralgia	
	synovitis	
	rhabdomyolysis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)	
Investigations	increased creatine kinase	positive antinuclear antibody
	increased bilirubin	
	increased liver transaminase (AST [SGOT], ALT [SGPT])	
	increased alkaline phosphatase	
	anaemia or severe anaemia	

Blood and lymphatic system disorders	leukopenia	
	eosinophilia	
	bone marrow hypoplasia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	
	thrombocytopenia	
Respiratory, thoracic and mediastinal disorders	laryngeal oedema	
Skin and subcutaneous tissue disorders	angioedema	anaphylaxis
	urticaria	lupus-like syndrome
	exfoliative dermatitis	vasculitis
	rash	alopecia
	dermatitis	
	pruritus	

Additional adverse reactions that have been reported included photosensitivity and cholecystitis. (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

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

Treatment of Overdosage

Symptomatic supportive measures should be taken should overdosage occur. Monitor liver and renal function. There is no antidote.

Consider administration of activated charcoal in the event of potentially toxic ingestion. Activated charcoal is most effective when administered within 1 hour of ingestion. In patients who are not fully conscious, or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Gemfibrozil's mechanism of action has not been definitely established. In man, gemfibrozil inhibits peripheral lipolysis and decreases the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. Gemfibrozil also inhibits synthesis and increases clearance of apolipoprotein B, which is a carrier of VLDL, leading to a decrease in VLDL production.

Gemfibrozil is a lipid regulating agent which decreases serum triglycerides and total cholesterol, and increases high density lipoprotein cholesterol (HDL-cholesterol). The lipid-lowering changes occur primarily in the very low density lipoprotein (VLDL) fraction rich in triglycerides and to a lesser extent in the low density

lipoprotein (LDL) fraction rich in cholesterol. Gemfibrozil treatment of patients with elevated triglycerides due to Type IV hyperlipoproteinaemia may cause a rise in LDL-cholesterol.

However, gemfibrozil increases the HDL-cholesterol subfractions, HDL2 and HDL3, as well as apolipoproteins AI and AII.

Clinical Trials

Helsinki Heart Study

Gemfibrozil is a lipid regulating agent which decreases serum triglycerides and very low density lipoprotein (VLDL) cholesterol, and increases high density lipoprotein (HDL) cholesterol. While modest decreases in total and low density lipoprotein (LDL) cholesterol may be observed with gemfibrozil therapy, treatment of patients with elevated triglycerides due to Type IV hyperlipoproteinaemia often results in a rise in LDL-cholesterol. LDL-cholesterol levels in Type IIb patients with elevations of both serum LDL-cholesterol and triglycerides are, in general, minimally affected by gemfibrozil treatment; however, gemfibrozil usually raises HDL-cholesterol significantly in this group. Gemfibrozil increases levels of high density lipoprotein (HDL) subfractions HDL2 and HDL3, as well as apolipoproteins AI and AII. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease.

In the Helsinki Heart Study, a large randomised double-blind, placebo-controlled, primary prevention trial in 4081 male patients between the ages of 40 and 55, gemfibrozil therapy was associated with significant reductions in total plasma triglycerides and a significant increase in high density lipoprotein cholesterol. Moderate reductions in total plasma cholesterol and low density lipoprotein cholesterol were observed for the gemfibrozil treatment group as a whole, but the lipid response was heterogeneous, especially among different Fredrickson Types. The study involved subjects with serum non-HDL-cholesterol of over 5.2 mmol/L and no previous history of coronary heart disease. Over the five-year study period, the gemfibrozil group experienced a 34% reduction in serious coronary events (sudden cardiac deaths plus fatal and nonfatal myocardial infarctions) compared to placebo. There was a 37% reduction in nonfatal myocardial infarction. There was no significant difference in death rate due to all causes between the gemfibrozil group and the placebo group.

Table 3. Number of patients in each treatment group (gemfibrozil and placebo) as per Fredrickson Type

	Fredrickson Type				
Treatment Group	**Type IIa**	**Type IIb**	**Type IV**	**Type V**	**Total Number**
Gemfibrozil	1293	570	182	1	2046
Placebo	1297	561	177	0	2035

The greatest reduction in the incidence of serious coronary events occurred in Type IIb patients who had elevations of both LDL-cholesterol and total plasma triglycerides. This subgroup of Type IIb gemfibrozil group patients had a lower mean HDL-cholesterol level at baseline than the Type IIa subgroup that had elevations of LDL-cholesterol and normal plasma triglycerides. The mean increase in HDL-cholesterol in this study was 12.6% compared to placebo. It is not clear to what extent the findings of the Helsinki Heart Study can be extrapolated to other segments of the dyslipidaemic population not studied or to other lipid-altering drugs.

Table 4. Changes from baseline in the gemfibrozil treatment group

% Change From Baseline in Gemfibrozil Group over 5-yr Period				
Serum Lipid Parameter	**Type IIa (n=1293)**	**Type IIb (n=570)**	**Type IV (n=182)**	**All Subjects (n=2046)***
Triglycerides	-26.3%	-44.3%	-49.9%	-37.3%
Total Cholesterol	-9.2%	-8.6%	-5.0%	-8.7%
LDL-Cholesterol	-11.4%	-4.1%	+4.8%	-8.2%
HDL-Cholesterol	+8.5%	+11.7%	+9.6%	+9.0%
Non-HDL-Cholesterol	-13.5%	-12.4%	-7.8%	-12.5%

* One subject was a Fredrickson Type V

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Gemfibrozil is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a biologic half-life of 1.5 hours following single doses and 1.3 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

Metabolism

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

Excretion

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

Long-term studies have been conducted in rats and mice at doses of 30 and 300 mg/kg/day. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign and malignant liver neoplasms. In male and female mice, there were no statistically significant differences from controls in the incidence of liver tumours, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumours at 1 and 10 times the human dose.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, pregelatinised maize starch, crospovidone, hyprolose, polysorbate 80, colloidal anhydrous silica, magnesium stearate, Opadry White OY-LS-28908 (ARTG PI No. 2596).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container: HDPE bottle with PP cap

Pack size: 60 tablets.

Australian Register of Therapeutic Goods (ARTG)

AUST R 61430 - LIPIGEM gemfibrozil 600mg tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

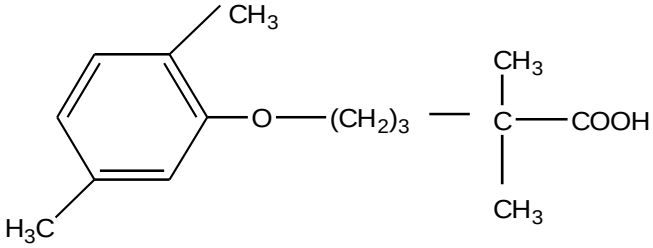
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid.

Structural formula :



Molecular formula : $C_{15}H_{22}O_3$

Molecular weight : 250.35

Gemfibrozil is a white, waxy powder which is stable under ordinary conditions. The melting point is 58-61°C. The solubility of gemfibrozil is 0.0019% (w/v) in water and in acid and over 1% in dilute base.

CAS Number

25812-30-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Limited trading as Viatris

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Millers Point NSW 2000

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

19/09/1997

10 DATE OF REVISION

04/06/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2	Minor editorial change to update excipient details
6.5	Minor editorial changes, Added AUST R details
8	Update to Sponsor details

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