

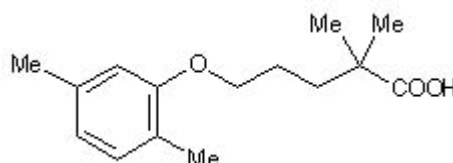
GEMFIBROZIL-GA

PRODUCT INFORMATION

NAME OF THE MEDICINE

GEMFIBROZIL-GA (gemfibrozil) 600 mg tablets

Chemical Structure:



CAS no. 25812-30-0 MW 250.3

DESCRIPTION

Gemfibrozil is a nonhalogenated phenoxy pentanoic acid. Its chemical name is 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid. It is a white, waxy powder which is stable under ordinary conditions. The melting point is 58 to 61°C. It is practically insoluble in water & acid, sparingly soluble in alkali, & freely soluble in methanol.

The other ingredients are: starch-pregelatinised maize, silica-colloidal anhydrous, hydroxypropylcellulose, polysorbate 80, cellulose microcrystalline, and calcium stearate in the tablet core while the coating contains opadry white Y-1R-7000B (consisting of hypromellose, Macrogol 4000, indigo carmine aluminium lake CI 73015 & titanium dioxide).

ACTIONS

Pharmacology: 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 & HDL₃, as well as apolipoproteins A1 & A11.

The mechanism of action of gemfibrozil has not been definitely established. In humans, gemfibrozil inhibits peripheral lipolysis & 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 VLDL cholesterol, and increases HDL cholesterol. While modest decreases in total & 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 & HDL₃, as well as apolipoproteins AI & AII. Epidemiological studies have shown that both low HDL cholesterol & 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 4,081 male patients between the ages of 40 & 55 years, gemfibrozil therapy was associated with significant reductions in total plasma triglycerides and a significant increase in HDL cholesterol. Moderate reductions in total plasma cholesterol and LDL 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 non-fatal myocardial infarctions) compared to placebo. There was a 37% reduction in non-fatal myocardial infarction. There was no significant difference in death rate due to all causes between the gemfibrozil and the placebo group.

Table 1

Treatment group	Fredrickson type				Total
	type IIa	type IIb	type IV	type V	
gemfibrozil	1,293	570	182	1	2,046
placebo	1,297	561	177	0	2,035

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 2: % change from baseline in gemfibrozil group over a 5 year period

Serum lipid parameter	type IIa (n=1,293)	type IIb (n=570)	type IV (n=182)	all subjects (n=2,046)*
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 IV

Pharmacokinetics. Gemfibrozil is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in 1 to 2 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.

Gemfibrozil mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and carboxyl metabolite. Approximately 70% of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. 6% of the dose is accounted for in the faeces.

INDICATIONS

An adjunct to diet and other therapeutic measures for the following:

- Severe hypertriglyceridemia (types IV and V) in persons 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, gall bladder 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: Gemfibrozil is indicated when exercise, weight loss and specific dietary or other non-drug measures such as limiting alcohol intake have failed. Other medical disorders such as hypothyroidism and diabetes should be controlled as much as possible.

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 deemed inadequate after three months.

CONTRAINDICATIONS

Hepatic or severe renal dysfunction, including primary biliary cirrhosis. Pre-existing gall bladder disease (see **Precautions**). Hypersensitivity to gemfibrozil. Pregnant or lactating women (see **Precautions**). Type I hyperlipoproteinaemia. Use of gemfibrozil with repaglinide. Concurrent use of cerivastatin, due to a risk of myopathy and rhabdomyolysis (see **Warnings** and **Interactions with other Medicines**)

WARNINGS 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 subjects and 300 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 for one year beyond. There was a statistically significant (29%) higher total mortality in the clofibrate treated than in the comparable placebo treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate treated subjects for gall bladder disease was confirmed.

During the Helsinki Heart Study and in the one and half year 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 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 a 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 gall bladder 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, gall bladder studies are indicated. Gemfibrozil therapy should be discontinued if gallstones are found.

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

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. 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 lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (see **Interactions with other Medicines**). 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 creatinine kinase level determination. If myositis is suspected or diagnosed, gemfibrozil therapy should be withdrawn.

The risk of serious toxicity is increased if gemfibrozil is used concomitantly with other fibrates. Such combination therapy should be used with caution and 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.

Carcinogenesis, mutagenesis, impairment of fertility: long-term studies have been conducted in rats and mice at doses of 30 and 300 mg / kg / day. The incidence of benign hepatic nodules and hepatic carcinomas was significantly increased in high dose male rats. The incidence of hepatic carcinomas also increased 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 hepatic neoplasms. In male and female mice, there was no statistically significant differences from controls in the incidence of hepatic 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 one and ten times the human dose.

Administration of approximately 2 times the human dose (based on surface area) to male rats for 10 weeks results 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.

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.

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

Impairment of fertility. 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 foetal wastage. Treated males were responsible for the reduced fertility rate, probably because of the marked suppression of weight gain they experienced.

PRECAUTIONS

Initial therapy: Before instituting gemfibrozil 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, eg diabetes mellitus or hypothyroidism.

Long term therapy: Because long-term administration of gemfibrozil is recommended, pre-treatment 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 gemfibrozil 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.

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, gall bladder studies are indicated. Therapy with gemfibrozil should be discontinued if gallstones are found.

Haematological changes: Mild haemoglobin, haematocrit and white cell decreases have been observed occasionally on initiating gemfibrozil therapy. However, these levels stabilise during long-term administration. Rarely, severe anaemia, leucopenia, thrombocytopenia and bone marrow hypoplasias have been reported. Therefore, periodic blood counts are recommended during the first 12 months of gemfibrozil administration.

Hepatic function: Abnormal liver function tests have been observed occasionally during gemfibrozil administration, including elevations of AST, ALT, LDH, and alkaline phosphatase. These are usually reversible when gemfibrozil is discontinued. Therefore, periodic liver function studies are recommended and gemfibrozil therapy should be terminated if abnormalities persist.

Hepatobiliary disease: In patients with a past history of jaundice or hepatic disorder, gemfibrozil should be used with caution.

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

Use in Pregnancy: (Category B3)

The physiological hyperlipidaemia of pregnancy does not require treatment.

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 foetus 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 foetuses from 22 litters of rabbits.

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

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.

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

ADVERSE 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 effects were statistically more frequent in subjects in the gemfibrozil group; expressed as gemfibrozil (n=2046) / placebo (2035). Gastrointestinal reactions (34.2% / 23.8%): dyspepsia 19.6% / 11.9%, abdominal pain 9.8% / 5.6%, acute appendicitis (histologically confirmed in most cases where data were available) 1.2% / 0.6%; atrial fibrillation 0.7% / 0.1%.

The following adverse events were reported in more than 1% of subjects but without a significant difference between groups. Diarrhoea 7.2% / 6.5%, fatigue 3.8% / 3.5%, nausea and / or 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 & 0.5% of placebo subjects, a 64% excess which is not statistically different from the excess of gall bladder surgery observed in the clofibrate compared to the placebo group in the WHO study. Nervous system & special senses adverse effects were more common in the gemfibrozil group. These included hypaesthesia, paraesthesia, and taste perversion. Other adverse effects that were more common among the gemfibrozil treatment group subjects but where a causal relationship was not established included cataracts, peripheral vascular disease, & intracerebral haemorrhage.

From other studies it seems probable that gemfibrozil is causally related to the occurrence of musculoskeletal symptoms (see **Warnings**), and to abnormal liver function tests and haematological changes (see **Precautions**).

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 effects 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 (s).

General. Weight loss.

Cardiac. Extrasystoles.

Gastrointestinal. Cholestatic jaundice*, cholelithiasis*; pancreatitis, hepatomas, colitis.

Central nervous system. Dizziness*, somnolence*, paraesthesia*, peripheral neuritis*, decreased libido*, depression*, headache*; confusions, convulsions, syncopes.

Ocular. Blurred vision*; retinal oedemas.

Genitourinary. Impotence*; decreased male fertility.

Musculoskeletal. Myopathy*, myasthenia*, myalgia*, painful extremities*, arthralgia*, synovitis*, rhabdomyolysis* (see **Warnings & Precautions**).

Clinical laboratory. Increased creatine phosphokinase*, increased bilirubin*, increased liver transaminase (AST, ALT)*, increased alkaline phosphatase*; positive antinuclear antibodies.

Haematological. Anaemia*, leucopenia*; thrombocytopenias.

Immunological. Angioedema*, laryngeal oedema*, urticaria*; anaphylaxis, lupus-like syndromes, vasculitis.

Dermatological. Exfoliative dermatitis*, rash*, dermatitis*, pruritis*; alopecias.

INTERACTIONS WITH OTHER MEDICINES

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 level has stabilised (see **Warnings**).

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 three 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 renal damage. (see **Warnings**).

Reduced Bioavailability of gemfibrozil may result when given simultaneously with colestipol. Administration of the drugs two hours or more apart is recommended.

DOSAGE AND ADMINISTRATION

Adults: The recommended dose for adults is 600 mg twice daily (total daily dose 1200 mg) administered ½ an hour before the morning & evening meal. For patients who cannot tolerate gemfibrozil when given half an hour before food, gemfibrozil may be taken with food. The bioavailability of gemfibrozil is higher when administered half an hour before food.

OVERDOSAGE

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.

Symptomatic supportive measures should be provided should overdosage occur.

PRESENTATION AND STORAGE CONDITIONS

GEMFIBROZIL-GA 600 mg tablets are a white, film coated, elliptical, biconvex, capsule shaped tablets engraved with 600, and a breakline on one face and plain on the other face.

GEMFIBROZIL-GA tablets are available in bottle of 60 tablets.

Store below 30°C.

POISONS SCHEDULE OF THE MEDICINE

Prescription Medicine (S4)

NAME AND ADDRESS OF THE SPONSOR

Ascent Pharma Pty Ltd
151-153 Clarendon Street
South Melbourne VIC 3205

GEMFIBROZIL-GA 600 mg AUST R 147595

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