PRODUCT INFORMATION

JEZIL® (gemfibrozil)

NAME OF MEDICINE

Gemfibrozil is a nonhalogenated phenoxypentanoic acid. The chemical name for Gemfibrozil is 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid (CAS Registry no. 25812-30-0), with the following structural formula:

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CH₃
CH₃
O-CH₂CH₃CH₂-COOH
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Molecular formula: C₁₅H₂₂O₃
Molecular weight: 250.35

DESCRIPTION

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

Each film-coated tablet contains 600 mg gemfibrozil. JEZIL tablets also contain colloidal anhydrous silica, pregelatinised starch, polysorbate 80, microcrystalline cellulose, hypromellose, calcium stearate, hydroxypropylcellulose, methyl hydroxybenzoate, propyl hydroxybenzoate, macrogol 3500, opaspray white and candelilla wax

PHARMACOLOGY

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.
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 HDL$_2$ and HDL$_3$, 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 randomized 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>
<thead>
<tr>
<th>Fredrickson Type</th>
<th>Treatment Group</th>
<th>Type IIA</th>
<th>Type IIB</th>
<th>Type IV</th>
<th>Type V</th>
<th>Total Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemfibrozil</td>
<td>1293</td>
<td>570</td>
<td>182</td>
<td>1</td>
<td>2,046</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1297</td>
<td>561</td>
<td>177</td>
<td>0</td>
<td>2,035</td>
<td></td>
</tr>
</tbody>
</table>

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.
% Change From Baseline in Gemfibrozil Group over 5-yr Period

<table>
<thead>
<tr>
<th>Serum Lipid Parameter</th>
<th>Type IIa (n=1,293)</th>
<th>Type IIb (n=570)</th>
<th>Type IV (n=182)</th>
<th>All Subjects (n=2,046)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>-26.3%</td>
<td>-44.3%</td>
<td>-49.9%</td>
<td>-37.3%</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>-9.2%</td>
<td>-8.6%</td>
<td>-5.0%</td>
<td>-8.7%</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>-11.4%</td>
<td>-4.1%</td>
<td>+4.8%</td>
<td>-8.2%</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>+8.5%</td>
<td>+11.7%</td>
<td>+9.6%</td>
<td>+9.0%</td>
</tr>
<tr>
<td>Non-HDL-Cholesterol</td>
<td>-13.5%</td>
<td>-12.4%</td>
<td>-7.8%</td>
<td>-12.5%</td>
</tr>
</tbody>
</table>

One subject was a Fredrickson Type V.

**Pharmacokinetics**

**Absorption** - Gemfibrozil is well absorbed from the gastro-intestinal 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.

**INDICATIONS**

Gemfibrozil 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:

GEMFIBROZIL 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 GEMFIBROZIL. THE DRUG SHOULD BE WITHDRAWN OR ADDITIONAL THERAPY INSTITUTED IF THE LIPID RESPONSE IS DEEMED INADEQUATE AFTER THREE MONTHS.

CONTRAINDICATIONS

- Hepatic dysfunction including primary biliary cirrhosis
- Severe renal dysfunction,
- Pre-existing gall bladder or biliary tract disease including gallstones (See PRECAUTIONS).
- Hypersensitivity to Gemfibrozil or any of the excipients in the formulation
- Patients with previous history of photoallergy or phototoxic reaction during treatment with fibrates
- Pregnant or lactating women
- Type I hyperlipoproteinaemia
- Concomitant use with repaglinide (see INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

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 vs 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). GI 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 % vs 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 vs 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. Gemfibrozil 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 the INDICATIONS section. If a significant serum response is not obtained, Gemfibrozil 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

There have been reports of severe myositis with markedly elevated creatine kinase and myoglobinuría (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 DRUG 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.

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, haematocrit 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, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Gemfibrozil administration.

Monitoring Liver function

Abnormal liver function tests have been observed occasionally during Gemfibrozil administration, including elevations of AST (SGOT), ALT (SGPT), LDH, and alkaline phosphatase. They 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.
**Monitoring Serum Levels**

**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 such as diabetes mellitus or hypothyroidism.

**Long-term therapy** - Because long-term administration of Gemfibrozil 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 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.

**CARCINOGENICITY, MUTAGENESIS, EFFECTS ON FERTILITY**

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.

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.

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.

**Effects on 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.
**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 foetus due to Gemfibrozil. Minor foetotoxicity 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 tumourigenic in male and 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.

The physiological hyperlipidaemia of pregnancy does not require treatment.

**Use during 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.

**INTERACTIONS WITH OTHER MEDICINES**

Caution should be exercised with concomitant use of Gemfibrozil with CYP2C8, CYP2C9, CYP2C19, CYP1A2, UGTA1 and UGTA3 substrates.

**Concomitant use with 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 PRECAUTIONS.

**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.

**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 and prolonged its hypoglycaemic effects. Co-administration of Gemfibrozil and repaglinide increases the risk for severe hypoglycaemia and is contraindicated (see CONTRAINDICATIONS).
**HMG-CoA Reductase**

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 PRECAUTIONS).

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 colestipol. Administration of the drugs two hours or more apart is recommended.

**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 reactions were statistically more frequent in subjects in the Gemfibrozil group:

<table>
<thead>
<tr>
<th></th>
<th>GEMFIBROZIL (N=2046)</th>
<th>PLACEBO (N=2035)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency in % of subjects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal reactions</td>
<td>34.2</td>
<td>23.8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>19.6</td>
<td>11.9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Acute appendicitis</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>(histologically confirmed in most cases where data were available)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Adverse events reported by more than 1 % of subjects, but without a significant difference between groups</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>2.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Eczema</td>
<td>1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Complaint</td>
<td>CAUSAL RELATIONSHIP PROBABLE</td>
<td>CAUSAL RELATIONSHIP NOT ESTABLISHED</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Rash</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Headache</td>
<td>1.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

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 PRECAUTIONS), and to abnormal liver function tests and haematologic 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 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 following).
<table>
<thead>
<tr>
<th>CAUSAL RELATIONSHIP PROBABLE</th>
<th>CAUSAL RELATIONSHIP NOT ESTABLISHED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourinary disorders</td>
<td>renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>renal failure as a consequence of rhabdomyolysis</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>myopathy</td>
</tr>
<tr>
<td></td>
<td>myasthenia</td>
</tr>
<tr>
<td></td>
<td>myalgia</td>
</tr>
<tr>
<td></td>
<td>painful extremities</td>
</tr>
<tr>
<td></td>
<td>arthralgia</td>
</tr>
<tr>
<td></td>
<td>synovitis</td>
</tr>
<tr>
<td></td>
<td>rhabdomyolysis (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>anaemia</td>
</tr>
<tr>
<td></td>
<td>leukopenia</td>
</tr>
<tr>
<td></td>
<td>eosinophilia</td>
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<tr>
<td></td>
<td>bone marrow hypoplasia (see PRECAUTIONS)</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>laryngeal oedema</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>exfoliative dermatitis</td>
</tr>
<tr>
<td></td>
<td>rash</td>
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<tr>
<td></td>
<td>dermatitis</td>
</tr>
<tr>
<td></td>
<td>pruritus</td>
</tr>
<tr>
<td></td>
<td>angioedema</td>
</tr>
<tr>
<td></td>
<td>urticaria</td>
</tr>
<tr>
<td>Investigations</td>
<td>increased creatine phosphokinase</td>
</tr>
<tr>
<td></td>
<td>positive antinuclear antibody</td>
</tr>
<tr>
<td></td>
<td>increased bilirubin</td>
</tr>
<tr>
<td></td>
<td>increased liver trans-aminase (AST[SGOT], ALT [SGPT])</td>
</tr>
<tr>
<td></td>
<td>increased alkaline phosphatase</td>
</tr>
</tbody>
</table>

Additional adverse reactions that have been reported included photosensitivity, cholecystitis see PRECAUTIONS.

**DOSAGE AND 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 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.

Use in Patients with Hepatic Dysfunction

Gemfibrozil is contraindicated in patients with hepatic dysfunction. See CONTRAINDICATIONS.

Use in Patients with Renal Dysfunction

Gemfibrozil is contraindicated in patients with severe renal dysfunction. See PRECAUTIONS and CONTRAINDICATIONS.

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 taken should overdosage occur. Monitor liver and renal function. There is no antidote.

Consider administration of activated charcoal in the event of a 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.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION & STORAGE CONDITIONS

JEZIL 600 mg tablets are white, oval shaped, film-coated tablet embossed with ‘PD737’ on one side.

Store below 30°C.

POISON SCHEDULE OF MEDICINES

S4

SPONSOR

Pfizer Australia Pty Limited
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Australia

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