

# New Zealand Data Sheet



## 1. PRODUCT NAME

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Lipazil® 600 mg tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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Each Lipazil 600 mg tablet contains 600 mg of gemfibrozil.

### Excipient(s) with known effect

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

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Lipazil 600 mg tablets are a white, film coated, elliptical, biconvex, tablets engraved with 600, breakline & dp logo on one face. The other face is plain.

## 4. CLINICAL PARTICULARS

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### 4.1. Therapeutic indications

Gemfibrozil is indicated in adults with the following dyslipidemias who have not responded to diet and other nonmedical measures:

- 1) Primary prevention of coronary heart disease and myocardial infarction in patients with hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia. Fredrickson's classification types IIa, IIb and IV respectively.
- 2) Treatment of other dyslipidemias
  - Fredrickson types III and V
  - Associated with diabetes
  - Associated with xanthomata
- 3) Hypertriglyceridemia regardless of type.
  - Elevated triglyceride levels of 11.29 mmol/L (1000 mg/dL) or above
  - Elevated triglyceride levels of 5.65 to 11.29 mmol/L (500-1000 mg/dL) as seen in diabetic patients with normal or low serum cholesterol.
  - Elevated triglyceride levels of 2.65 to 5.65 mmol/L (200-500 mg/dL) in patients with risk factors such as smoking hypertension, obesity, and diabetes and after all attempts to remove these risks factors have failed.

## **4.2. Dose and method of administration**

### **Dose**

#### ***Adults***

The recommended dose of Lipazil for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. The maximum recommended daily dose is 1500 mg.

#### ***Use in children***

The safety and efficacy of gemfibrozil has not been established in children and its use in this age group is therefore not recommended.

## **4.3. Contraindications**

- Hepatic or renal dysfunction, including primary biliary cirrhosis
- Pre-existing gallbladder disease (refer to section 4.4)
- Hypersensitivity to gemfibrozil
- The drug should not be used in pregnant or lactating patients
- Gemfibrozil is not indicated for the treatment of Type I hyperlipoproteinemia

## **4.4. Special warnings and precautions for use**

### **Initial Therapy**

Before instituting gemfibrozil therapy, attempts should be made to control serum lipids and lipoproteins with appropriate diet, exercise, and weight loss or other nondrug measures like limiting alcohol intake. Other medical disorders like diabetes and hypothyroidism must be controlled as much as possible.

### **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 hyperlipoproteinemic patients.

### **Continued Therapy**

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

### **Seasonal Variations of Lipid Levels**

Gemfibrozil is not expected to alter seasonal variations of peak serum cholesterol values in mid-winter and late summer or the decreases in autumn and spring.

### **Haemoglobin Changes**

A mild haemoglobin or haematocrit decrease has been observed in occasional patients following initiation of gemfibrozil therapy. The levels then stabilise during long-term administration. Rarely severe anaemia, thrombocytopenia, leukopenia and bone marrow hypoplasia have been reported. Therefore, a blood count is recommended every two months during the first 12 months of gemfibrozil administration.

### **Liver Function**

Abnormal liver function tests have been observed occasionally during gemfibrozil administration, including elevations of AST, ALT, LDH, alkaline phosphatase and bilirubin rarely have been reported. 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 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.

### **Cholelithiasis**

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.

## **4.5. Interaction with other medicines and other forms of interaction**

### **HMG-CoA reductase inhibitors**

Lovastatin should not be used concomitantly with gemfibrozil, due to the possibility of rhabdomyolysis. This can occur as soon as three weeks or several months after initial combined therapy has begun. In most patients who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy 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. A similar interaction with other HMG-CoA reductase inhibitors cannot be excluded.

### **Anticoagulants**

Caution should be exercised when anticoagulants are given in conjunction with gemfibrozil. The dosage of 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.

## **Laboratory tests**

There have been reports of increased alkaline phosphatase, increased bilirubin, increased liver transaminase (AST, ALT), and an increase creatine phosphokinase. These are usually reversible when gemfibrozil is discontinued. It is advisable to carry out periodic liver function studies. Gemfibrozil should be discontinued if abnormalities persist.

### **4.6. Fertility, pregnancy and lactation**

#### **Pregnancy**

Category B3.

The physiological hyperlipidaemia of pregnancy does not require treatment. The safety in human pregnancy has not been established. Reproduction studies have been performed in rats and rabbits. No evidence of impaired fertility in females or harm to the fetus due to gemfibrozil were noted. Minor fetotoxicity manifested by reduced birth rates was observed at the highest dose levels. Amongst almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits no significant malformations were found. No studies have been done on pregnant women. Because of the fact that gemfibrozil is tumorigenic 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 fetus.

#### **Lactation**

It is not known whether gemfibrozil is excreted in human milk. Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

#### **Fertility**

Refer to 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 affect the ability to drive or operate machinery.

### **4.8. Undesirable effects**

In the double-blind controlled phase of the Helsinki Heart Study a total of 4081 male patients took part ranging in age from 40 to 55 years. Of these 2046 patients received gemfibrozil and 2035 received the placebo.

The following adverse effects were statistically more frequent in subjects taking gemfibrozil.

#### **Table 1**

	<b>Gemfibrozil (N=2046)</b>	<b>Placebo (N=2035)</b>
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (historically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1

NOTE: Results shown as frequency in percent of subjects.

Adverse events reported by more than 1% of subjects but without a significant difference between groups.

**Table 2**

	<b>Gemfibrozil (N=2046)</b>	<b>Placebo (N=2035)</b>
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

NOTE: Results shown as frequency in percent of subjects.

Additional adverse reactions that have been reported where a causal relationship to treatment with gemfibrozil is probable: cholestatic jaundice, cholelithiasis, dizziness, somnolence, paraesthesia, peripheral neuritis, decreased libido, depression, blurred vision, impotence, myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis, anaemia, leucopenia, angioedema, laryngeal oedema, urticaria, exfoliative dermatitis, dermatitis and pruritus.

### ***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

### **4.9. Overdose**

In one case of overdose where a child ingested 9g of gemfibrozil non-specific symptoms of nausea and vomiting were reported. Symptomatic supportive measures should be taken should overdosage occur.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5. PHARMACOLOGICAL PROPERTIES

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### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Serum-lipid lowering agent, ATC code: C10AB04

#### **Action**

Gemfibrozil is a lipid regulating agent, which decreases serum triglycerides and total cholesterol, and increases high density lipoprotein cholesterol.

The lipid-lowering changes occur primarily in the very low-density lipoprotein (VLDL) fraction (Sf 20-400) rich in triglycerides and to a lesser extent in the low-density lipoprotein (LDL) fraction (Sf 0-20) rich in cholesterol. Gemfibrozil treatment of patients with elevated triglycerides due to Type IV hyperlipoproteinemia may cause a rise in LDL-cholesterol. In addition, gemfibrozil increases the high-density lipoprotein (HDL) cholesterol subfractions, HDL2 and HDL3, as well as apolipoproteins AI and AII.

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

Animal studies suggest that gemfibrozil may, in addition to elevating HDL cholesterol (HDL-C), reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the faeces.

Maximal effects on serum lipids may take many months to achieve. But therapeutic responses are observed within two months.

Serum lipid parameters return to pre-treatment levels within two months of discontinuing gemfibrozil.

#### **Helsinki Heart Study**

The Helsinki Heart study produced a significant reduction in total plasma triglycerides, total and low-density lipoprotein cholesterol and a significant increase in high density lipoprotein cholesterol. Over the 5-year study period the gemfibrozil group showed a 34% reduction in the overall incidence to coronary heart disease (in years 3 and 5 of the study the reduction in coronary heart disease was greater than 50%). There was a 7% decrease in non-fatal myocardial infarction and a 26% decrease in cardiac deaths. The subjects included in the study had no previous history of coronary heart disease. The overall difference in the incidence of coronary

heart disease was significantly lower for gemfibrozil treated patients than those receiving the placebo ( $p < 0.02$ , two tailed).

## **5.2. Pharmacokinetic properties**

Gemfibrozil is well absorbed from the gastrointestinal tract following oral administration. Gemfibrozil is metabolised to a high extent in the liver. Two hours after taking gemfibrozil approximately 70% of the dose is excreted in the urine, primarily as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. Six percent of the dose is accounted for in the faeces. Peak plasma levels occur in one to two hours following single doses. The mean half-life is approximately 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. The volume of distribution is approximately 0.2L/kg. The extent of protein binding is about 97%.

There are four other metabolites which are available to a lesser extent. One of these metabolites has hypolipaeamic activity similar to gemfibrozil but is available in trace amounts. Three metabolic pathways have been identified. The first metabolic pathway is that of conjugation of gemfibrozil and its metabolites. The second, and presumably the principal route, involves hydroxylation of the metamethyl group of gemfibrozil, yielding a benzyl alcohol (Metabolite II) that undergoes rapid oxidation to a benzoic acid metabolite (Metabolite III, the major metabolite). The third pathway involves hydroxylation of the aromatic ring to a phenol (Metabolite I) which is further converted to Metabolite IV, a compound with no intact carboxylic acid function but which is phenolic in nature. (General introduction, information about whether the medicine is a pro-drug or whether there are active metabolites, chirality, solubility, information on the population in which general pharmacokinetic data were obtained, etc.)

## **5.3. Preclinical safety data**

Long-term studies with gemfibrozil have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas was increased also in low dose males, but the increase was not statistically significant ( $p > 0.05$ ). There were no statistically significant differences from controls in the incidence of liver tumours in female rats and in male and female mice. Liver and testicular cell tumours were increased in male rats. The relevance of these findings to humans is not known. Because of the above findings, use of gemfibrozil should be limited to those patients specified in the Indications section (please refer to section 4.1).

Electron microscopy studies demonstrate a florid hepatic peroxisome proliferation following gemfibrozil administration to male rats. These changes have not been found in human liver yet, which suggests that changes in the male rat may not be predictive of human response. Male rats had a dose related increase in benign Leydig cell tumours.

Subcapsular bilateral cataracts occurred in 10% and unilateral in 6.3% of high dose male rats.

Gemfibrozil was administered in oral doses of approximately 95 and 325mg/kg/day to male and female rats for 61 days and 15 days respectively before mating. Dosing was continued throughout the pregnancy and weaning of the offspring. Gemfibrozil produced dose related suppression in fertility, but this had no effect of the length of gestation, duration of parturition, size of litter or embryonic or foetal wastage. The reduced fertility rate was due to the treated male rats, which is probably due to the marked suppression of weight gain experienced.

## **6. PHARMACEUTICAL PARTICULARS**

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### **6.1. List of excipients**

Lipazil tablet contains calcium stearate, colloidal silicon dioxide, hypolose, microcrystalline cellulose, Opadry white Y-IR-7000B, polysorbate 80 and pregelatinised maize starch.

### **6.2. Incompatibilities**

Not applicable.

### **6.3. Shelf life**

3 years

### **6.4. Special precautions for storage**

Store at or below 30°C. Protect from light and moisture.

### **6.5. Nature and contents of container**

HDPE bottle pack, 60 tablets.

### **6.6. Special precautions for disposal and other handling**

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## **7. MEDICINE SCHEDULE**

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Prescription medicine

## **8. SPONSOR**

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Douglas Pharmaceuticals Ltd  
P O Box 45 027  
Auckland 0651  
New Zealand  
Phone: (09) 835 0660



## 9. DATE OF FIRST APPROVAL

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17 December 2009

## 10. DATE OF REVISION OF THE TEXT

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08 February 2019

Summary table of changes

<b>Section Changed</b>	<b>Summary of new information</b>
All	SPC format