

pharmaniaga®



SAFFID CAPSULE 300MG

PRODUCT DESCRIPTION

A maroon and white 'O' size elongated capsule containing white powder.

Each hard capsule contains Gemfibrozil 300mg

PHARMACODYNAMICS

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

Gemfibrozil's mechanism of action has not been definitively established. In man, gemfibrozil stimulates the peripheral lipolysis of triglyceride rich lipoproteins such as Very Low-Density Lipoprotein (VLDL) and chylomicrons (by stimulation of Lipoprotein Lipase). Gemfibrozil also inhibits synthesis of VLDL in the liver. Gemfibrozil increases the High-Density Lipoprotein 2 (HDL₂) and High-Density Lipoprotein 3 (HDL₃) subfractions as well as apolipoprotein A-I and A-II.

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

PHARMACOKINETICS

Absorption

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

Distribution

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

Metabolism

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

elimination pathway for gemfibrozil in man.

The enzymes involved in the metabolism of gemfibrozil are not known. The interaction profile of gemfibrozil and its metabolites is complex. *In vitro* and *in vivo* studies have shown that gemfibrozil inhibits CYP2C8, CYP2C9, CYP2C19, CYP1A2, UGT1A1, UGT1A3 and OATP1B1. Gemfibrozil 1-O-β-glucuronide also inhibits CYP2C8 and OATP1B1.

Elimination

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

Special patient groups

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

INDICATIONS

Gemfibrozil is used in conjunction with dietary modification in the treatment of type IIa, type IIb, type III, type IV and type V hyperlipoproteinaemia. It is also indicated for the primary prevention of ischaemic heart disease in hyperlipidaemic patients who have not responded to dietary and other measures; in the USA this use is restricted to type IIb patients who also have low HDL cholesterol concentrations.

RECOMMENDED DOSE

Usual adult dose:

Orally 4 capsules (1.2 g) a day in two divided dose thirty minutes before the morning and evening meals.

Usual paediatric dose:

Dosage has not been established.

ROUTE OF ADMINISTRATION

Oral.

CONTRAINDICATIONS

Gemfibrozil is contraindicated in patients:

- hypersensitive to gemfibrozil
- with hepatic impairment
- with severe renal impairment
- with history of or have pre-existing gall bladder or biliary tract disease, including gallstones
- with previous history of photoallergy or phototoxic reaction during treatment with fibrates

WARNINGS AND PRECAUTIONS

Muscle disorders (myopathy/rhabdomyolysis)

There have been reports of myositis, myopathy and markedly elevated creatine phosphokinase associated with gemfibrozil. Rhabdomyolysis has also been reported rarely. Muscle damage must be considered in any patient presenting with diffuse myalgia, muscle tenderness and/or marked increase in muscle CPK levels (>5x ULN); under these conditions, treatment must be discontinued.

Concomitant HMG CoA reductase inhibitors

The concomitant administration of gemfibrozil with simvastatin 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. Pharmacokinetic interactions may also be present and dosage adjustments may be necessary.

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

A creatine phosphokinase (CPK) level should be measured before starting such a combination in patients with predisposing factors for rhabdomyolysis as follows:

- renal impairment
- hypothyroidism
- alcohol abuse
- age > 70 years
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another fibrate or HMG-CoA reductase inhibitor

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

Use in patients with gallstone formation

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

Monitoring serum lipids

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

Monitoring liver function

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

Monitoring Blood Counts

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

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

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS

- Repaglinide. Co-administration with gemfibrozil or with gemfibrozil and itraconazole prolonged its hypoglycaemic effects. Therefore, co-administration of gemfibrozil and repaglinide increases the risk for severe hypoglycaemia and is contraindicated.
- Dasabuvir. Co-administration of gemfibrozil with dasabuvir increased dasabuvir AUC and C_{max} due to CYP2C8 inhibition. Increased dasabuvir exposure may increase the risk of QT prolongation, therefore, co-administration of gemfibrozil with dasabuvir is contraindicated.
- Selixipag. Co-administration of gemfibrozil

200mm

210mm

200mm

with selexipag, a substrate for CYP2C8, doubled exposure (AUC) to selexipag and increased exposure (AUC) to the active metabolite, ACT-333679, by approximately 11-fold. Concomitant administration of gemfibrozil with selexipag is contraindicated.

- Enzalutamide, given in a single dose of 160 mg after gemfibrozil 600 mg twice daily, the AUC of enzalutamide plus active metabolite (N-desmethyl enzalutamide) was increased by 2.2-fold and corresponding C_{max} was decreased. Increased enzalutamide exposure may increase the risk of seizures. Concomitant treatment of gemfibrozil and enzalutamide should be avoided; if co-administration is considered necessary, the dose of enzalutamide should be reduced.
- 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.
- HMG CoA reductase inhibitors. The concomitant administration of gemfibrozil with simvastatin is contraindicated. The combined use of gemfibrozil and a statin should generally be avoided. The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse events, including rhabdomyolysis, has been reported when fibrates are co-administered with statins. Concurrent use of fibrates with HMG-CoA reductase inhibitors may cause severe myositis and myoglobinuria.
- Anticoagulants. Gemfibrozil may potentiate the effects of coumarin type vitamin K antagonist anticoagulants such as warfarin, acenocoumarol, and or phenprocoumon. The concomitant administration of gemfibrozil with these anticoagulants necessitates careful monitoring of prothrombin time (INR - International Normalised Ratio). Caution should be exercised when such a coumarin type vitamin K antagonist anticoagulant is given concomitantly with gemfibrozil. The dosage of the anticoagulant may need to be reduced to maintain desired prothrombin time levels.
- Bexarotene. Concomitant administration of gemfibrozil with bexarotene is not recommended as it results in substantial increase in plasma concentrations of bexarotene.
- Bile acid binding resins. Reduced bioavailability of gemfibrozil may result when given simultaneously with resin-granule drugs such as colestipol. Administration of the

products two hours or more apart is recommended.

- Colchicine. Risk of myopathy and rhabdomyolysis may be increased with concomitant administration of colchicine and gemfibrozil. This risk may be increased in the elderly and in patients with hepatic or renal dysfunction. Clinical and biological monitoring are recommended, especially at the start of combined treatment.
- CYP2C8, CYP2C9, CYP2C19, CYP1A2, UGT1A1, UGT1A3 and OATP1B1 substrates. Gemfibrozil potently inhibits CYP2C8, CYP2C9, CYP2C19, CYP1A2, and UDP glucuronyltransferase (UGT1A1 and UGT1A3) enzymes and also inhibits organic anion-transporting polypeptide 1B1 (OATP1B1). In addition, gemfibrozil is metabolised to gemfibrozil 1-O- β -glucuronide which also inhibits CYP2C8 and OATP1B1.
- 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.
- Dietary sodium. This medicinal product contains less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets should be informed that this medicinal product is essentially 'sodium-free'.
- Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other drugs. Refer to the package insert for the other co-administered drugs before starting therapy with gemfibrozil.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate data on use of gemfibrozil in pregnant women and the potential risk is unknown. Thus, gemfibrozil should not be used during pregnancy unless the benefit outweighs the risk.

Lactation

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

ADVERSE EFFECTS

These adverse reactions do not usually lead to discontinuation of the treatment.

Blood and Lymphatic system disorder

Rare: Bone marrow failure, severe anemia, thrombocytopenia, leukopenia, eosinophilia

Psychiatric disorder

Rare: Depression, decreased libido

Nervous system disorder

Common: Vertigo, headache

Rare: Neuropathy peripheral, paraesthesia, dizziness, somnolence

Eye disorder

Rare: Vision blurred

Cardiac disorder

Uncommon: Atrial fibrillation

Respiratory, thoracic and mediastinal disorder

Rare: Laryngeal oedema

Gastrointestinal disorder

Very common: Dyspepsia

Common: Diarrhea, vomiting, nausea, abdominal pain, constipation, flatulence
Rare: Pancreatitis, appendicitis

Hepatobiliary disorder

Rare: Jaundice cholestatic, hepatitis, cholelithiasis, cholecystitis, hepatic function abnormal

Skin and Subcutaneous tissue disorder

Common: Eczema, rash

Rare: Angioedema, dermatitis exfoliative, urticaria, dermatitis, alopecia, photosensitivity reaction, pruritus

Musculoskeletal and connective tissue disorder

Rare: Rhabdomyolysis, myopathy, myositis, muscular weakness, synovitis, myalgia, arthralgia, pain in extremity

Reproductive system and breast disorder

Rare: Erectile dysfunction

General disorders and administration site conditions

Common: Fatigue

Investigations

Rare: Hemoglobin decreased, hematocrit decreased, white blood cell count decreased, blood creatine phosphokinase increased.

OVERDOSE AND TREATMENT

Symptoms reported with overdosage were abdominal cramps, abnormal Liver Function Test (LFT), diarrhea, increased Creatine Phosphokinase (CPK), joint and muscle pain, nausea and vomiting. Symptomatic supportive measures should be taken if overdose occurs.

STORAGE CONDITION

Store below 30°C.

SHELF LIFE

Product should not be used beyond the expiry date imprinted on the product packaging.

PACK SIZE

In blisters of 3 x 10's

REGISTRATION NUMBER

MAL22106021AZ

CONTROLLED MEDICINE

UBAT TERKAWAL

KEEP MEDICINES OUT OF REACH OF CHILDREN

JAUHI UBAT-UBATAN DARI KANAK-KANAK

For further information, please consult your doctor or your pharmacist.

Revision number : 01

Revision date : 01 Jul 2026

PRODUCT REGISTRATION HOLDER AND MANUFACTURER

INSPIRAPHARMA SDN. BHD. (200401023395)

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08000 SUNGAI PETANI,

KEDAH DARUL AMAN, MALAYSIA.

Lt-315.01

210mm