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(For Export Only)
110(L) x 260(H)mm
Draft (6) 22 Apr 2019

BROZIL FILM COATED TABLET 600MG

Ingredient(s):
Each tablet contains:
Gemfibrozil ……..…….....……..….....…….. 600mg

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 VLDL and cholymicrons (by stimulation of LPL). Gemfibrozil also inhibits synthesis of VLDL in the liver. Gemfibrozil increases the HDL2 and HDL3 subfractions as well as apolipoprotein A-I and A-II.

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 Cmax in the range 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%.

Biotransformation
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 mother 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, UGTA1, UGTA3 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. Six percent 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.

Indication(s):
It is effective in the following lipid disorders :
(i) Fredrickson Type IIa,IIb,III,IV & V;
(ii) Hyperlipidemia associated with diabetes;
(iii) For the prevention of coronary heart disease.

Dosage and Administration:
1200 mg(2 tablets) per day in 2 divided doses, 30 minutes before the morning and evening meals.
Some patients will experience therapeutic effect on 900mg/day; a few may require 1500 mg/day for satisfactory results.
To be dispensed on physician's prescription.

Route of administration:
Oral

Contraindication(s):
- Hypersensitivity to the active substance or to any of the excipients stated
- Hepatic impairment
- Severe renal impairment
- History of/or pre-existing gall bladder or biliary tract disease, including gallstones
- Concomitant use of repaglinide, dasabuvir, selexipag or simvastatin
- Patients with previous history of photoallergy or phototoxic reaction during treatment with fibrates
- Alcoholism
- Avoided during pregnancy and lactation.

Warnings and Precautions:
Before instituting gemfibrozil therapy, attempts should be made to control serum lipids with appropriate diet, exercise, cessation of smoking, limitation of alcohol intake, weight loss in obese patients, and treatment of the causes of secondary hyperlipidaemias such as hypothyroidism and diabetes mellitus.

Since long-term administration of gemfibrozil is recommended, all baseline values including lipid profile, blood count and liver fucntion tests, should be measured before treatment and periodic determinations of serum lipids should be withdrawn or additional therapy instituted if the lipid response is in inadequate after 3 months. In addition gemfibrozil should be withdrawn if after 3 months the response is paradoxical. Paradoxical response has been occasionally observed, usually in patients with alcoholic hepatic disease. The blood level of LDL cholesterol occasionally rises on treatment with gemfibrozil. A further estimation of LDL Cholesterol should therefore be made during treatment to confirm that the desired therapeutic effect has been achieved.

Safety and efficacy of Gemfibrozil in children younger than 18 years of age have not been established.

<u>Muscle disorders (myopathy/rhabdomyolysis)</u>
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.

<u>Concomitant HMG CoA reductase inhibitors</u>
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 concomitantl. 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 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

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 risks of severe myopathy, rhabdomyolysis and acute renal failure.

<u>Use in patients with gallstone formation</u>
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.

<u>Monitoring serum lipids</u>
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.

<u>Monitoring liver function</u>
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.

Interactions with other medicinal products
Concomitant use with CYP2C8, CYP2C9, CYP2C19, CYP1A2, UGTA1, UGTA3 and OATP1B1 substrates
The interaction profile of gemfibrozil is complex resulting in increased exposure of many medicinal products if administered concomitantly with gemfibrozil.
Gemfibrozil potently inhibits CYP2C8, CYP2C9, CYP2C19, CYP1A2, and UDP glucuronyltransferase (UGTA1 and UGTA3) 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.

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.

Concomitant anticoagulants
Gemfibrozil may potentiate the effects of coumarin type vitamin K antagonist anticoagulants such as warfarin, acenocoumarol, 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.

Interactions with Other Medicaments:
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.
Gemfibrozil has also been reported to influence the pharmacokinetics of simvastatin, lovastatin, pravastatin and rosuvastatin

Anticoagulants
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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 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.
Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other drugs.

Resin granule drugs, such as colestipol, administered at the same time may lead to reduced Gemfibrozil bioavailability. Separating taking the drugs by two hours or more is recommended.

The interaction profile of gemfibrozil is complex. Co-administration of gemfibrozil with repaglinide, dasabuvir or selexipag is contraindicated. The combination of gemfibrozil with rosiglitazone should be approached with caution.

Side Effects:
Most commonly reported adverse reactions are of gastrointestinal character. These adverse reactions do not usually lead to discontinuation of the treatment.

System Organ Class	Undesirable effect
Blood and lymphatic system disorders	
Rare	Bone marrow failure, severe anaemia, thrombocytopenia, leukopenia, eosinophilia
Psychiatric disorders	
Rare	Depression, decreased libido
Nervous system disorders	
Common	Vertigo, headache
Rare	Neuropathy peripheral, paraesthesia, dizziness, somnolence
Eye disorders	
Rare	Vision blurred
Cardiac disorders	
Uncommon	Atrial fibrillation
Respiratory, thoracic and mediastinal disorders	
Rare	Laryngeal oedema
Gastrointestinal disorders	
Very common	Dyspepsia
Common	Diarrhoea, vomiting, nausea, abdominal pain constipation, flatulence
Rare	Pancreatitis, appendicitis
Hepatobiliary disorders	
Rare	Jaundice cholestatic, hepatitis, cholelithiasis, cholecystitis, hepatic function abnormal
Skin and subcutaneous tissue disorders	
Common	Eczema, rash
Rare	Angioedema, dermatitis exfoliative, urticaria, dermatitis, alopecia, photosensitivity reaction, pruritus
Musculoskeletal and connective tissue disorders	
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	Haemoglobin decreased, haematocrit decreased, white blood cell count decreased, blood creatine phosphokinase increased

Symptoms and Treatment for Overdosage, and Antidote(s):
Symptoms of overdose include severe stomach pain with nausea & vomiting, muscle pain or weakness. If patient receive this symptoms, evaluation for gallstones and myositis is recommended. Symptoms and supportive treatment should be taken when an overdose occurs.

Storage Condition(s):
Store at temperature below 30ºC. Protect from light and moisture.

Shelf-Life:
3 years from the date of manufacture.

Product Description and Packing(s):
A white elliptical film coated tablets, one side impressed with a score.
Blister packing of 10's x 10.

Manufacturer and Product Registration Holder:
Y.S.P. INDUSTRIES (M) SDN. BHD. (192593 U)
Lot 3, 5 & 7, Jalan P/7, Section 13,
Kawasan Perindustrian Bandar Baru Bangi,
43000 Kajang, Selangor Darul Ehsan, Malaysia.
Ordering Line: 1 800 88 3027
Product Info: 1 800 88 3679

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