1. NAME OF THE MEDICINAL PRODUCT

Gemfibrozil Alternova 600 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg gemfibrozil.

Excipient: Lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, oblong, film-coated tablets inscription G 600

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Gemfibrozil Alternova is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:

Treatment of dyslipidemia
Mixed dyslipidaemia characterised by hypertri glyceridaemia and/or low HDL-cholesterol. Primary hypercholesterolaemia, particularly when a statin is considered inappropriate or is not tolerated.

Primary prevention
Reduction of cardiovascular morbidity in males with increased non-HDL cholesterol and at high risk for a first cardiovascular event, particularly when a statin is considered inappropriate or is not tolerated (see section 5.1).

4.2. Posology and method of administration

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. Gemfibrozil Alternova should be taken orally.

Adult
The dose range is 900 mg to 1200 mg daily.
The only dose with documented effect on morbidity is 1200 mg daily.

The 1200 mg dose is taken as 600 mg twice daily, half an hour before breakfast and half an hour before the evening meal.

The 900 mg dose is taken as a single dose half an hour before the evening meal.

Elderly (over 65 years old)
As for adults

Children and adolescents
Gemfibrozil therapy has not been investigated in children. Due to the lack of data the use of Gemfibrozil Alternova in children is not recommended.

Renal impairment
In patients with mild to moderate renal impairment (Glomerular filtration rate 50 - 80 and 30 - < 50 ml/min/1.73 m², respectively), start treatment at 900 mg daily and assess renal function before increasing dose. Gemfibrozil Alternova should not be used in patients with severely impaired renal function (see section 4.3).

Hepatic impairment
Gemfibrozil is contraindicated in hepatic impairment (see section 4.3).

4.3. Contraindications

Hypersensitivity to gemfibrozil or any of the excipients.
Hepatic impairment.
Severe renal impairment.
History of/or pre-existing gall bladder or biliary tract disease, including gallstones.
Concomitant use of repaglinide (see section 4.5).
Patients with previous history of photoallergy or phototoxic reaction during treatment with fibrates.

4.4. Special warnings and precautions for use

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 use of HMG CoA reductase inhibitors
The risk of muscle damage may be increased in the event of combination with an HMG-CoA reductase inhibitor. Pharmacokinetic interactions may also be present (see also section 4.5) 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.

**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 (see section 4.8).

**Interactions with other medicinal products (see also sections 4.3 and 4.5)**

*Concomitant use with CYP2C8, CYP2C9, CYP2C19, CYP1A2, UGTA1 and UGTA3 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, UGTA1 and UGTA3 enzymes (see section 4.5)

*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 use with oral anticoagulants*

Gemfibrozil may potentiate the effects of oral anticoagulants, which necessitates careful monitoring of the anticoagulant dosing. Caution should be exercised when anticoagulants are given in conjunction with gemfibrozil. The dosage of the anticoagulant may need to be reduced to maintain desired prothrombin time levels (see Section 4.5.)

*Lactose*

The product contains lactose. It is therefore not suitable for patients with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5. Interaction with other medicinal products and other forms of interaction
The interaction profile of gemfibrozil is complex. In vivo studies indicate that gemfibrozil is a potent inhibitor of CYP2C8 (an enzyme important for the metabolism of e.g. repaglinide, rosiglitazone and paclitaxel). In vitro studies have shown that gemfibrozil is a strong inhibitor of CYP2C9 (an enzyme involved in the metabolism of e.g. warfarin and glimepiride), but also of CYP 2C19, CYP1A2, UGTA1 and UGTA3 (see Section 4.4).

**Repaglinide**

The combination of gemfibrozil with repaglinide is contra-indicated (see Section 4.3). Concomitant administration has resulted in 8-fold increase in repaglinide plasma concentration probably by inhibition of the CYP2C8 enzyme, resulting in hypoglycaemic reactions.

**Rosiglitazone**

The combination of gemfibrozil with rosiglitazone should be approached with caution. Coadministration with rosiglitazone has resulted in 2.3-fold increase in rosiglitazone systemic exposure, probably by inhibition of the CYP2C8 isozyme (see section 4.4).

**HMG CoA reductase inhibitors**

The combined use of gemfibrozil and a statin should generally be avoided (see section 4.4). 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. Gemfibrozil caused an almost 3-fold increased in AUC of simvastatin acid possibly due to inhibition of glucoronidation via UGTA1 and UGTA3, and a 3-fold increase in pravastatin AUC which may be due to interference with transport proteins. One study indicated that the co-administration of a single rosuvastatin dose of 80 mg to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in a 2.2-fold increase in mean $C_{\text{max}}$ and a 1.9-fold increase in mean AUC of rosuvastatin.

**Oral anticoagulants**

Gemfibrozil may potentiate the effects of oral anticoagulants, which necessitates careful monitoring of the anticoagulant dosing (see section 4.4).

**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.

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

### 4.6. Pregnancy and lactation

**Pregnancy**
There are no adequate data on use of gemfibrozil in pregnant women. Animal studies are insufficiently clear to allow conclusions to be drawn on pregnancy and foetal development (see section 5.3). The potential risk for humans is unknown. Gemfibrozil should not be used during pregnancy unless it is clearly necessary.

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

### 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 negatively influence driving.

### 4.8 Undesirable effects

Most commonly reported adverse reactions are of gastrointestinal character and are seen in approximately 7% of the patients. These adverse reactions do not usually lead to discontinuation of the treatment.

Adverse reactions are ranked according to frequency using the following convention: Very common (> 1/10), Common (> 1/100, < 1/10), Uncommon (> 1/1,000, < 1/100), Rare (> 1/10,000, < 1/1,000), Very rare (< 1/10,000), including isolated reports:

**Platelet bleeding and clotting disorders**
Rare: thrombocytopenia.

**Red blood cell disorders**
Rare: severe anaemia. Self-limiting, mild haemoglobin and haematocrit decrease have been observed on initiating gemfibrozil therapy.

**White cell and reticuloendothelial system disorders**
Rare: leucopenia, eosinophilia, bone marrow hypoplasia. Self-limiting, white cell decrease has been observed on initiating gemfibrozil therapy.

**Central and peripheral nervous system**
Common: vertigo, headache.
Rare: dizziness, somnolence, paresthesia, peripheral neuritis, depression, decreased libido.

**Vision disorders**
Rare: blurred vision.

**Heart rate and rhythm disorders**
Uncommon: atrial fibrillation.

**Gastro-intestinal system disorders**
Very common: dyspepsia.
Common: abdominal pain, diarrhoea, flatulence, nausea, vomiting, constipation.
Rare: pancreatitis, acute appendicitis.
Liver and biliary system disorders
Rare: cholestatic jaundice, disturbed liver function, hepatitis, cholelithiasis, cholecystitis.

Skin and appendages disorders
Common: eczema, rash.
Rare: exfoliative dermatitis, dermatitis, pruritus, alopecia.

Musculoskeletal disorders
Rare: arthralgia, synovitis, myalgia, myopathy, myasthenia, painful extremities and myositis accompanied by increase in creatine kinase (CK), rhabdomyolysis.

Urinary system disorders
Rare: impotence.

Body as a whole-general disorders
Common: fatigue.
Rare: photosensitivity, angioedema, laryngeal edema, urticaria.

4.9 Overdose

Overdose has been reported. Symptoms reported with overdosage were abdominal cramps, abnormal LFT’s, diarrhoea, increased CPK, joint and muscle pain, nausea and vomiting. Non-specific symptoms reported were nausea and vomiting. The patients fully recovered. Symptomatic supportive measures should be taken if overdose occurs.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Serum-lipid lowering agent
Chemical subgroup: Fibrates

ATC code: C10A B04

Gemfibrozil is a non-halogenated phenoxy pentanoic 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 chylomicrons (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.

Animal studies suggest that the turnover and removal of cholesterol from the liver is increased by gemfibrozil.

In the Helsinki Heart Study, which was a large placebo-controlled study with 4081 male subjects, 40 to 55 years of age, with primary dyslipidaemia (predominantly raised non-HDL cholesterol +/- hypertriglyceridaemia), but no previous history of coronary heart disease, gemfibrozil 600 mg twice daily produced a significant reduction in total plasma triglycerides, total and low density lipoprotein cholesterol and a significant increase in high density lipoprotein cholesterol. The cumulative rate of cardiac end-points (cardiac death and non-fatal myocardial infarction) during a
5 year follow-up was 27.3/1000 in the gemfibrozil group (56 subjects) and 41.4/1000 in the placebo group (84 subjects) showing a relative risk reduction of 34.0% (95% confidence interval 8.2 to 52.6, p < 0.02) and an absolute risk reduction of 1.4% in the gemfibrozil group compared to placebo. There was a 37% reduction in non-fatal myocardial infarction and a 26% reduction in cardiac deaths. The number of deaths from all causes was, however, not different (44 in the gemfibrozil group and 43 in the placebo group). Diabetes patients and patients with severe lipid fraction deviations showed a 68% and 71% reduction of CHD endpoints, respectively.

5.2. Pharmacokinetic properties

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 \( C_{\text{max}} \) in the range 15 to 25 mg/ml 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. The enzymes involved in the metabolism of gemfibrozil are not known. The interaction profile of gemfibrozil is complex (see sections 4.3, 4.4 and 4.5). In vitro and in vivo studies have shown that gemfibrozil inhibits CYP2C8, CYP2C9, CYP2C19, CYP1A2, UGTA1 and UGTA3.

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.

5.3 Preclinical safety data

In a 2-year study of gemfibrozil, subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3%, of male rats treated at 10 times the human dose.

In a mouse carcinogenicity study at dosages corresponding to 0.1 and 0.7 times the clinical exposure (based on AUC), there were no significant differences from controls in the incidence of tumors. In a rat carcinogenicity study at dosages corresponding to 0.2 and 1.3 times the clinical exposure (based on AUC), the incidence of benign liver nodules and liver carcinomas was
significantly increased in high dose males, and the incidence of liver carcinomas increased also in the low dose males, but this increase was not statistically significant.

Liver tumors induced by gemfibrozil and other fibrates in small rodents are generally considered to be related to the extensive proliferation of peroxisomes in these species and, consequently, of minor clinical relevance.

In the male rat, gemfibrozil also induced benign Leydig cell tumors. The clinical relevance of this finding is minimal.

In reproductive toxicity studies, administration of gemfibrozil at approximately 2 times the human dose (based on body surface area) to male rats for 10 weeks resulted in decreased fertility. Fertility was restored after a drug-free period of 8 weeks. Gemfibrozil was not teratogenic in either rats or rabbits. Administration of 1 and 3 times the human dose (based on body surface area) of gemfibrozil to female rabbits during organogenesis caused a dose-related decrease in litter size. Administration of 0.6 and 2 times the human dose (based on body surface area) of gemfibrozil to female rats from gestation Day 15 through weaning caused dose-related decreases in birth weight and suppression of pup growth during lactation. Maternal toxicity was observed in both species and the clinical relevance of decreases in rabbit litter size and rat pup weight is uncertain.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinized maize starch, silicon dioxide, sodium potato starch glycolate, polysorbate, microcrystalline cellulose, magnesium stearate, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol, lactose.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

Container: Keep the container tightly closed in order to protect from light and moisture.

Blister: Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Container (PE) of 98 and blister (PVC/PVDC/Al) of 28, 30, 50, 56, 60, 90, 98, 100 or 196 film-coated tablets (600 mg).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

version 2007/07/07
No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Alternova A/S
Industriparken 23-25
2750 Ballerup
Denmark

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT