ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Austria	Pfizer Corporation Austria Ges.m.b.H Seidengasse 33 - 35 A – 1070 Wien	Gevillon	450 mg	Film coated tablets	Oral use
Austria	Pfizer Corporation Austria Ges.m.b.H Seidengasse 33 - 35 A – 1070 Wien	Gevillon	900 mg	Film coated tablets	Oral use
Belgium	Pfizer S.A. Rue Léon Theodor 102 B – 1090 Bruxelles	Lopid	300 mg	Capsules	Oral use
Belgium	Pfizer S.A. Rue Léon Theodor 102 B – 1090 Bruxelles	Lopid	600 mg	Film-coated tablets	Oral use
Belgium	Pfizer S.A. Rue Léon Theodor 102 B – 1090 Bruxelles	Lopid	900 mg	Film-coated tablets	Oral use
Denmark	Pfizer ApS Lautrupvang 8 DK – 2750 Ballerup	Lopid	300 mg	Capsules	Oral use
Denmark	Pfizer ApS Lautrupvang 8 DK – 2750 Ballerup	Lopid	450 mg	Film-coated tablets	Oral use
Denmark	Pfizer ApS	Lopid	600 mg	Film-coated tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Lautrupvang 8 DK – 2750 Ballerup				
Finland	Pfizer Oy P.O. Box 45 FIN – 02601 Espoo	Lopid	300 mg	Capsules	Oral use
Finland	Pfizer Oy P.O. Box 45 FIN – 02601 Espoo	Lopid	600 mg	Film-coated tablets	Oral use
France	Pfizer 23-25 Avenue Du Dr. Lannelongue F – 75014 Paris	Lipur	450 mg	Film-coated tablets	Oral use
Germany	Parke-Davis GmbH Pfizerstrasse 1 D – 76139 Karlsruhe	Gevilon	450 mg	Film-coated tablets	Oral use
Germany	Parke-Davis GmbH Pfizerstrasse 1 D – 76139 Karlsruhe	Gevilon	600 mg	Film-coated tablets	Oral use
Germany	Parke-Davis GmbH Pfizerstrasse 1 D – 76139 Karlsruhe	Gevilon uno	900 mg	Film-coated tablets	Oral use
Germany	Parke-Davis GmbH Pfizerstrasse 1 D – 76139 Karlsruhe	Continulipid	450 mg	Film-coated tablets	Oral use
Germany	Parke-Davis GmbH Pfizerstrasse 1	Continulipid	600 mg	Film-coated tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	D – 76139 Karlsruhe				
Greece	Pfizer Hellas A.E. Alketou Street 5 116-33 Athens	Lopid	600 mg	Film-coated tablets	Oral use
Greece	Pfizer Hellas A.E. Alketou Street 5 116-33 Athens	Lopid	900 mg	Film-coated tablets	Oral use
Iceland	Pfizer ApS Lautrupvang 8 DK – 2750 Ballerup	Lopid	300 mg	Capsules	Oral use
Iceland	Pfizer ApS Lautrupvang 8 DK – 2750 Ballerup	Lopid	450 mg	Film-coated tablets	Oral use
Iceland	Pfizer ApS Lautrupvang 8 DK – 2750 Ballerup	Lopid	600 mg	Film-coated tablets	Oral use
Ireland	Warner Lambert UK Ltd trading as: Parke Davis Lambert Court Chestnut Avenue Eastleigh Hampshire SO53 3ZQ United Kingdom	Lopid	300 mg	Capsules	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Ireland	Warner Lambert UK Ltd trading as: Parke Davis Lambert Court Chestnut Avenue Eastleigh Hampshire SO53 3ZQ United Kingdom	Lopid	600 mg	Film coated tablets	Oral use
Italy	Pfizer Italia S.r.l. Via Valbondione 113 I – 00188 Roma	Lopid	600 mg	Tablets	Oral use
Italy	Pfizer Italia S.r.l. Via Valbondione 113 I – 00188 Roma	Lopid	900 mg	Tablets	Oral use
Italy	Pfizer Italia S.r.l. Via Valbondione 113 I – 00188 Roma	Lopid TC	900 mg	Granules	Oral use
Italy	Pfizer Italia S.r.l. Via Valbondione 113 I – 00188 Roma	Lopid TC	1200 mg	Granules	Oral use
Luxembourg	Pfizer S.A. Rue Léon Theodor 102 B – 1090 Bruxelles	Lopid	300 mg	Capsules	Oral use
Luxembourg	Pfizer S.A. Rue Léon Theodor 102 B – 1090 Bruxelles	Lopid	600 mg	Film-coated tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
Luxembourg	Pfizer S.A. Rue Léon Theodor 102 B – 1090 Bruxelles	Lopid	900 mg	Film-coated tablets	Oral use
Netherlands	Pfizer BV Postbus 37 NL – 2900 AA Capelle a/d Ijssel	Lopid	600 mg	Coated tablets	Oral use
Netherlands	Pfizer BV Postbus 37 NL – 2900 AA Capelle a/d Ijssel	Lopid	900 mg	Coated tablets	Oral use
Portugal	Laboratórios Pfizer, Lda., Lagoas Park - Edifício nº 10 2740-244 Porto Salvo	Lopid	300 mg	Capsules	Oral use
Portugal	Laboratórios Pfizer, Lda., Lagoas Park - Edifício nº 10 2740-244 Porto Salvo	Lopid	600 mg	Coated tablets	Oral use
Portugal	Laboratórios Pfizer, Lda., Lagoas Park - Edifício nº 10 2740-244 Porto Salvo	Lopid	900 mg	Coated tablets	Oral use
Spain	Parke-Davis, S.L. (Pfizer Group) Av. de Europa 20-B Parque Empresarial La Moraleja 28108 Alcobendas (Madrid)	Lopid	600 mg	Tablets	Oral use
Spain	Parke-Davis, S.L. (Pfizer Group) Av. de Europa 20-B	Lopid	900 mg	Tablets	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration
	Parque Empresarial La Moraleja 28108 Alcobendas (Madrid)				
Sweden	Pfizer AB Nytorpsvägen 36 Box 501 S – 183 25 Täby	Lopid	300 mg	Capsules	Oral use
Sweden	Pfizer AB Nytorpsvägen 36 Box 501 S – 183 25 Täby	Lopid	450 mg	Film coated tablets	Oral use
Sweden	Pfizer AB Nytorpsvägen 36 Box 501 S – 183 25 Täby	Lopid	600 mg	Film coated tablets	Oral use
United Kingdom	Warner Lambert UK Ltd trading as: Parke Davis Lambert Court Chestnut Avenue Eastleigh,Hampshire SO53 3ZQ United Kingdom	Lopid	300 mg	Capsules	Oral use
United Kingdom	Warner Lambert UK Ltd trading as: Parke Davis Lambert Court Chestnut Avenue Eastleigh,Hampshire SO53 3ZQ United Kingdom	Lopid	600 mg	Film coated tablets	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF LOPID AND ASSOCIATED NAMES (see Annex I)

- Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (section 6).

- Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Section 4.1 Therapeutic Indications

The MAH was requested to propose and scientifically justify a common EU wide approach as there were divergences between national approvals regarding the use of Lopid in:

- The treatment of hyperlipoproteinaemia,
- The primary prevention of cardiovascular morbidity.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Lopid, the following was considered to be the most suitable harmonised Section 4.1 indications text:

Currently, statins are the first-line treatment for patients with lipid abnormalities where pharmacological intervention has been definitely associated with a beneficial outcome. The statins have shown convincing efficacy regarding both primary and secondary prevention of cardiac mortality and morbidity. Treatment with gemfibrozil should be considered mainly in situations were statins may not be used such as intolerance to statins or in patients with particular lipid disorders. In addition, the unrestricted recommendation to use a product which is not a statin to treat patients with dyslipoproteinaemia of Fredrickson types II a and b (and probably also type III) does not reflect the current practice.

The inclusion of the Fredrickson classification in the wording of the indication was questioned by the CPMP, partly due to the fact that this classification is becoming obsolete.

Finally, the harmonized indication is in line with European and US guidelines for the management of lipid disorders, which requires both confirmation of diagnosis by laboratory testing and lifestyle modification before initiating lipid-lowering treatment.

- **Treatment of dyslipidaemia**

The mechanism of action of gemfibrozil has not been definitively established. In man, gemfibrozil stimulates the peripheral lipolysis of triglyceride rich lipoproteins such as very low-density lipoproteins (VLDL) and chylomicrons (by stimulation of the lipoprotein lipase, LPL). Gemfibrozil also inhibits synthesis of VLDL in the liver. Gemfibrozil increases the high-density lipoproteins HDL_2 and HDL_3 subfractions as well as apolipoprotein A-I and A-II.

The statins are now the primary choice in patients with hypercholesterolemia due to the superior low-density lipoproteins (LDL)-cholesterol lowering properties and the demonstrated benefit in outcome. Due to the increased risk of muscular disorders, combined use of gemfibrozil and statins is no longer

recommended and therefore the use of gemfibrozil is primary reserved for those patients with dyslipidaemia characterised by high triglyceride levels and/or low HDL cholesterol levels. This was shown by two outcome-studies conducted with gemfibrozil (known as the Helsinki Heart and the Veterans Affairs HDL Intervention Trial [denoted by VA-HIT] studies). The Helsinki Heart study was published by Frick MH, Elo O, Haapa K et al. Helsinki Heart Study: primary prevention with gemfibrozil in middle aged men with dyslipidemia. N Engl J Med 1987;317:1237-1245. The VA-HIT study was published by Rubins HB, Robins SJ, Collins D et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999; 341:410-418.

In a subgroup analysis of the Helsinki Heart Study it was found that gemfibrozil was particularly effective in preventing heart disease in patients with high serum triglyceride concentrations, plus either low HDL-cholesterol or a high LDL/HDL cholesterol ratio (Circulation 1992; 85: 37). In the second outcome study, the VA-HIT study, gemfibrozil resulted in a significant reduction in the risk of major cardiovascular events in patients with coronary heart disease whose primary lipid abnormality was a low HDL cholesterol, with LDL-cholesterol levels considered normal (≤ 3.6 mmol/l).

Gemfibrozil is therefore particularly indicated for patients with high triglycerides and/or low HDL-cholesterol. Hypercholesterolemia still is an indication, but mainly in combination with such dyslipidaemia.

- **Primary prevention (Reduction of cardiovascular morbidity)**

This indication is mainly based on 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.

The study is only carried out in men between 40 and 55 years of age in a Finland, where at that time men were at particularly high risk for ischemic heart disease. This hampers the external validity to the general population.

Patients were selected on the basis of non-HDL cholesterol with an acceptance level ≥ 5.2 mmol/l without specifying levels of LDL- and HDL-cholesterol and triglycerides), Subgroup analysis showed that benefit was most pronounced in the patients who probably fitted more in the patients with hypertriglyceridaemia and mixed dyslipidaemia than in those with hypercholesterolemia. Statins are the products of choice to treat patients with isolated hypercholesterolemia.

4.1 Therapeutic indications

Lopid 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 hypertriglyceridaemia 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).

Section 4.2. Posology and method of administration

Not all strengths were authorised in all Member States. Little divergences were identified between dose recommendations. More importantly, no Member States recommended a maximum dose <1,200 mg/day (the dose used in Helsinki Heart Trial). Where a maximum dose was recommended, it was consistently 1,500 mg.

The MAH was requested to substantiate scientifically the divergent information across member states and justify a proposed common wording, especially with regard to therapeutic daily dose range.

It was proposed to rationalise the authorised strengths of Lopid. The 1200mg tablet and sachet formulations have already been and will be removed from the market. Therefore the 300 mg capsule and 450 mg, 600 mg and 900 mg tablets will still be authorised. The recommended dosage is 1200 mg per day with a 900 mg minimum dose and a maximum recommended dose of 1500 mg. Medical practice over the years has established the use of combinations of the smaller dosage sizes to achieve the recommended daily dose even though higher strengths have been approved.

The proposed posology fits into the current recommendations. In addition to the recommended maintenance dose, the CPMP considered it appropriate to recommend both a minimum and a maximum dose as well. As the two major clinical outcome studies, Helsinki Heart Study and the VA-HIT study have been carried out with a 1200 mg daily dose (2x600 mg), the CPMP considered that 1200 mg should be the recommended daily dose. Some recommendations were introduced for patients with patients with mild to moderate renal impairment.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Lopid the following was considered to be the most suitable harmonised Section 4.2 Posology and method of administration text:

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. Lopid 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 Lopid 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 m^2, respectively), start treatment at 900 mg daily and assess renal function before increasing dose. Lopid 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).

- Safety issues

Section 4.3 Contraindications

The MAH was requested to propose and scientifically justify a common EU wide approach as the contraindications text was nor harmonised between Member States especially relating to the use in patients with:

- (severe) liver and renal disease and gallbladder disease.

A recently reported drug interaction with repaglinide has been added to the contraindications. The combination of gemfibrozil with repaglinide resulted in an 8-fold increased exposure of repaglinide, resulting in hypoglycaemia.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Lopid, the following was considered to be the most suitable harmonised Section 4.3 Contraindications:

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.

Section 4.4. Special warnings and precautions for use

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Lopid, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (See Annex III). The risk of muscle disorders (myopathy/rhabdomyolysis) and the special warnings and special precautions for use in case of concomitant administration of HMG CoA reductase inhibitors were further emphasised in the harmonised SPC. In addition, recently reported interactions with other medicinal products have been added to the SPC for Lopid.

Section 4.5. Interaction with other medicinal products and other forms of interaction

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Lopid, the most suitable harmonised Section 4.5 Interaction with other medicinal products and other forms of interaction (See Annex III). In addition,

recently reported interactions with other medicinal products have been added to the SPC for Lopid. The risk of interaction with other medicinal products (esp. with those products metabolised through CYP2C9 and CYP2C8) was further emphasised in the harmonised SPC.

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

Finally, the CPMP considered that all presentations may be useful to treat the patients in the approved indications.

Benefit/Risk considerations

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Lopid is favourable for use relating to:

Lopid 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 hypertriglyceridaemia 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).

GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,
- Important new information on interactions with several medicinal products was included in the SPC,

the CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion for Lopid and associated names (see Annex I). The divergences identified at the start of the referral have been resolved.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was Annexed to the Commission Decision on this Article 30 referral for gemfibrozil containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<(LOPID and associated names)> <(strength)> mg <tablets> <capsules> <granules> <film-coated tablets> <coated tablets>

[See Annex I. To be implemented nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 300 mg gemfibrozil.
Each film-coated tablet contains 450 mg, 600 mg or 900 mg gemfibrozil.
For excipients, see 6.1.

[See Annex I. To be implemented nationally]

3. PHARMACEUTICAL FORM

<Capsule> <Film-coated tablet> <Tablet> <Granules> <Coated tablet>

[See Annex I. To be implemented nationally]

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Lopid 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 hypertriglyceridaemia 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. Lopid 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 Lopid 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 m^2, respectively), start treatment at 900 mg daily and assess renal function before increasing dose. Lopid 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 special 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 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

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 oral anticoagulants
Gemfibrozil may potentiate the effects of oral anticoagulants, which necessitates careful monitoring of the anticoaglant 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.)

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 and 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. Co-administration 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 simvaststin, 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_{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.

4.6. Pregnancy and lactation

Pregnancy
There are no adequate data on use of Lopid 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. Lopid should not be used during pregnancy unless it is clearly necessary.

Lactation
There are no data on excretion of gemfibrozil in milk. Lopid 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: leucopoenia, 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, 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. 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 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 HDL_2 and HDL_3 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_{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 excreteed 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 tumours 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

[To be implemented nationally]

6.2 Incompatibilities

[To be implemented nationally]

6.3 Shelf life

[To be implemented nationally]

6.4 Special precautions for storage

[To be implemented nationally]

6.5 Nature and contents of container

Not all pack sizes may be marketed
[To be implemented nationally]

6.6 Instructions for use and handling

[To be implemented nationally]

7. MARKETING AUTHORIZATION HOLDER

[To be implemented nationally]

8. MARKETING AUTHORIZATION NUMBER

[To be implemented nationally]

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

[To be implemented nationally]

10. DATE OF (PARTIAL) REVISION OF THE TEXT

