SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lovastatin 20/40 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20/40 mg lovastatin.

Excipients with known effect:
Lactose monohydrate
Each tablet contains 139/278 mg Lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

20 mg: Round, slightly biconvex, light blue tablets with bevelled edge and a score on one side, diameter 8 mm.
40 mg: Round, slightly biconvex, light green tablets with bevelled edge and a score on one side, diameter 11 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The reduction of elevated total and LDL cholesterol concentrations in plasma in combination with the dietary treatment in cases, when the patient has primary hypercholesterolaemia and diet and other non-pharmacological measures alone have proven insufficient. The reduction of elevated cholesterol concentration in plasma in combined hypercholesterolaemia and hypertriglyceridaemia when the elevated cholesterol concentration in plasma is the primary reason for the treatment.

4.2 Posology and method of administration

The patient should be placed on a standard cholesterol-lowering diet before receiving lovastatin and should continue on this diet during treatment with lovastatin. Any cause for secondary hypercholesterolaemia should be excluded before initiation of treatment.

Posology

Hypercholesterolaemia
The usual starting dose is 20 mg/day given as a single dose with the evening meal. Single daily doses given with the evening meal have been shown to be more effective than the same dose given with the morning meal, perhaps because cholesterol is synthesised mainly at night. Patients with mild to moderate hypercholesterolaemia can be treated with a starting dose of 10 mg of lovastatin. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg daily, given in single or divided doses with the morning and evening meals. Divided doses (i.e., twice daily) tend to be slightly more effective than single daily doses.

The dosage of lovastatin should be reduced, if LDL-cholesterol levels fall below 75 mg/dl (1.94 mmol/l) or the total cholesterol levels fall below 140 mg/dl (3.6 mmol/l).

Coronary atherosclerosis
In the coronary atherosclerosis trials which utilised lovastatin with or without concomitant therapy, the dosages used were 20 to 80 mg daily, given in single or divided doses. In the two trials which utilised lovastatin alone, the dose was reduced if total plasma cholesterol decreased to below 110 mg/dl (2.85 mmol/l) or if LDL-cholesterol decreased to below 80 mg/dl (2.1 mmol/l), respectively.

Concomitant therapy
Lovastatin is effective alone or in combination with bile-acid sequestrants.

In patients taking cyclosporin, danazol, gemfibrozil, other fibrates or lipid-lowering doses (≥ 1 g/day) of niacin concomitantly with lovastatin, the dose of lovastatin should not exceed 20 mg/day. In patients taking amiodarone or verapamil concomitantly with lovastatin, the dose of lovastatin should not exceed 40 mg/day (see sections 4.4 and 4.5).

Special populations

Dosage in renal insufficiency
Because lovastatin does not undergo significant renal excretion, modification of dosage should not be necessary in patients with moderate renal insufficiency.
In patients with severe renal insufficiency (creatinine clearance < 30 ml/min), dosages above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of lovastatin in children has not yet been established. Currently available data are described in section 4.8 and section 5.1 but no recommendation on a posology can be made.

Older People
In one controlled study in older people over the age of 60 years, efficacy appeared similar to that seen in the population as a whole, and there was no apparent increase in the frequency of clinical or laboratory adverse findings.

Method of administration

The tablets should be swallowed whole, without chewing, with a sufficient amount of liquid with the meal.

If the response to the diet and to other non-pharmacological measures is insufficient, the treatment of primary hypercholesterolaemia usually requires long-term therapy with lovastatin.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Active liver disease or unexplained persistent elevation of serum transaminases
- Pregnancy and lactation (see section 4.6)
- Cholestasis
- Myopathy
- Concomitant administration of potent CYP3A4 inhibitors (e. g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, delavirdine, erythromycin, clarithromycin, telithromycin and nefazodone) (see section 4.5).

4.4 Special warnings and precautions for use

Myopathy/Rhabdomyolysis
Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10 x the upper limit of normal

(ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

The risk of myopathy/rhabdomyolysis is increased by concomitant use of lovastatin with the following:

Potent inhibitors of CYP3A4, e.g., itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors (e.g. nelfinavir) or nefazodone, particularly with higher doses of lovastatin (see below and section 4.5).

Lipid-lowering drugs that can cause myopathy when given alone: gemfibrozil, other fibrates, or lipid-lowering doses (≥1 g/day) of niacin, particularly with higher doses of lovastatin (see below and sections 4.2 and 4.5).

Other drugs:

Cyclosporine or danazol: Particularly with higher doses of lovastatin (see section 4.5).

Amiodarone or verapamil: The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class (see section 4.5).

Fusidic acid: Lovastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.
Statin therapy may be re-introduced seven days after the last dose of fusidic acid.
In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of lovastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical study (EXCEL) in which patients were carefully monitored and some interacting drugs were excluded, there was one case of myopathy among 4,933 patients randomised to lovastatin 20-40 mg daily for 48 weeks, and 4 among 1,649 patients randomised to 80 mg daily.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Creatine kinase measurement
Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes interpretation of the CK values difficult. If CK levels are significantly elevated at baseline (> 5 x ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Before the treatment
All patients starting therapy with lovastatin, or whose dose of lovastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

Caution should be exercised in patients with pre-disposing factors for rhabdomyolysis. In order to establish a reference baseline value, a CK level should be measured before starting a treatment in the following situations:

- Elderly (age > 70 years)
- Renal impairment

- Uncontrolled hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If a patient has previously experienced a muscle disorder on a fibrate or a statin, treatment with a different member of the class should only be initiated with caution. If CK levels are significantly elevated at baseline (> 5 x ULN), treatment should not be started.

While on treatment
If muscle pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CK levels should be measured. If these levels are found, in the absence of strenuous exercise, to be significantly elevated (> 5 x ULN), treatment should be stopped. If muscular symptoms are severe and cause daily discomfort, even if CK levels are < 5 x ULN, treatment discontinuation may be considered. If myopathy is suspected for any other reason, treatment should be discontinued.

If symptoms resolve and CK levels return to normal, then re-introduction of the statin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

Therapy with lovastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Consequently:

1. Use of lovastatin concomitantly with potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors [e.g. nelfinavir] or nefazodone) should be avoided (see sections 4.3 and 4.5). If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment. Concomitant use with other medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

2. The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine, danazol, gemfibrozil, other fibrates or lipid-lowering doses ($\geq$ 1 g/day) of niacin. The combined use of lovastatin with gemfibrozil should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. The benefits of the use of lovastatin in patients receiving other fibrates, niacin, cyclosporine, or danazol should be carefully weighed against the risks of these drug combinations (see sections 4.2 and 4.5.). Addition of fibrates or niacin to lovastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates or niacin with low doses of lovastatin have been used without myopathy in small, short-term clinical studies with careful monitoring.

3. The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy (see sections 4.2 and 4.5).

4. All patients starting therapy with lovastatin, or whose dose of lovastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Lovastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and/or a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with lovastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

5. Many of the patients who have developed rhabdomyolysis on therapy with lovastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with lovastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Hepatic effects
In the initial clinical trials, marked (to more than 3 times the ULN) increases in transaminases occurred in a few patients, usually appearing 3 to 12 months after the start of therapy with lovastatin, but without the development of jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed mild focal hepatitis. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol. In patients in whom the drug was interrupted or discontinued because of raised transaminases, including the patient who underwent liver biopsy, the transaminase levels fell slowly to pretreatment levels.
In the 48-week EXCEL study performed in 8,245 patients, the incidence of marked (more than 3 times the ULN) increases in serum transaminases on successive testing was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day and 1.5% at 80 mg/day in patients on lovastatin.
It is recommended that liver function tests be performed prior to initiation of therapy in patients with a history of liver disease, or when otherwise clinically indicated. It is recommended that liver function tests be performed in all patients prior to use of 40 mg or more daily and thereafter when clinically indicated.
Should serum transaminase levels rise to more than three times the ULN, the potential risk of continuing lovastatin should be weighed against the anticipated benefits. Transaminase measurements should be repeated promptly; if these elevations are persistent or progressive, the drug should be discontinued.
As with other lipid-lowering agents, moderate (less than three times the ULN) elevations of serum transaminases have been reported during therapy with lovastatin (see section 4.8). These changes appeared soon after initiation of therapy with lovastatin, were usually transient, and were not accompanied by any symptoms; interruption of treatment was not required.
The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained persistent elevations of serum transaminases are contraindications to the use of lovastatin (see section 4.3).

Ophthalmic evaluations
In the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of aging. Long-term data from clinical trials do not indicate an adverse effect of lovastatin on the human lens.

Vitamin K antagonists
There is a risk for increased effect of vitamin K antagonists (see section 4.5).

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Homozygous familial hypercholesterolaemia
In patients with the rare homozygous familial hypercholesterolaemia, lovastatin was less effective, possibly because these patients have no functional LDL receptors. Lovastatin appears to be more likely to raise serum transaminases (see section 4.8) in these homozygous patients.

Hypertriglyceridaemia
Lovastatin has only a moderate triglyceride-lowering effect and it is not indicated where hypertriglyceridaemia is the abnormality of most concern (i.e. hyperlipidaemia types I, IV and V).

Diabetes Mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Impaired renal function

Lovastatin should be used with caution in severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.2).

Secondary hypercholesterolaemia
In case of secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, first treat the underlying disease.

Paediatric population
In limited controlled studies (see sections 4.8 and 5.1), there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. Adolescent females should be counselled on appropriate contraceptive methods while on lovastatin therapy (see sections 4.3 and 4.6). Lovastatin has not been adequately studied in pre-pubertal children or pre-menarchal girls, nor in patients younger than 10 years of age.

Excipient(s)
Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium (component of Quinoline Yellow)
Lovastatin 40 mg tablets contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 interactions
Lovastatin is metabolised by CYP3A4, but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolised by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of lovastatin (see sections 4.4. and 5.2). These inhibitors include itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, delavirdine and the antidepressant nefazodone.

Concomitant treatment with ketoconazole, itraconazole, posaconazole, HIV protease inhibitors, delavirdine, erythromycin, clarithromycin, telithromyicin or nefazodone is therefore contraindicated (see section 4.3). If treatment with ketoconazole, itraconazole, posaconazole, erythromycin, clarithromycin and telithromyicin is unavoidable, therapy with lovastatin must be temporarily suspended. Caution should be exercised when combining lovastatin with other less potent CYP3A4-inhibitors: cyclosporin and verapamil (see sections 4.2 and 4.4).

Interactions with lipid-lowering drugs that can cause myopathy when given alone
The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent inhibitors of CYP3A4, but which can cause myopathy when given alone (see section 4.4). These inhibitors include gemfibrozil, other fibrates and niacin (nicotinic acid) ($\geq$ 1 g/day).

Other drug interactions
Cyclosporin: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporin particularly with higher doses of lovastatin (see sections 4.2 and 4.4). Therefore, the dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporin. Although the mechanism is not fully understood, it has been shown that cyclosporin increases the AUC of HMG-CoA reductase inhibitors. The increase in the AUC of lovastatin acid is presumably due, in part, to inhibition of CYP3A4.

Danazol: The risk of myopathy and rhabdomyolysis is increased by concomitant administration of danazol particularly with higher doses of lovastatin (see sections 4.2 and 4.4).

Amiodarone or verapamil: The risk of myopathy/ rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class (see section 4.4).

The dosage of lovastatin should therefore not exceed 40 mg/day unless the clinical benefit does not outweigh the increased risk of myopathy or rhabdomyolysis.

Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.
If treatment with systemic fusidic acid is necessary, lovastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. Also see section 4.4.

Other interactions
Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs metabolised by CYP3A4. The effect of typical consumption (one 250 ml glass daily) is minimal (34% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration time curve) and of no clinical relevance. However, very large quantities (over 1 liter daily) significantly increase the plasma level of HMG-CoA reductase inhibitory activity during lovastatin therapy and should be avoided.

Coumarin derivatives
When lovastatin and coumarin anticoagulants are administered concomitantly, prothrombin time may be increased in some patients. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Propranolol
No clinically significant pharmacokinetics or pharmacodynamic interactions have been observed between propranolol and concomitantly administrated lovastatin.

Digoxin
In hypercholesterolaemic patients no influence on the digoxin plasma levels has been observed during a concomitant administration of lovastatin and digoxin.

Other concomitant therapy
Clinical studies have shown that a concurrent administration of lovastatin and ACE-inhibitors, beta-blockers, calcium-antagonists (except verapamil), diuretics, non-steroidal anti-inflammatory agents and antidiabetic medicinal products (glibenclamide, glipizide, insulin) has not caused clinically relevant interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
Lovastatin is contraindicated during pregnancy.

Safety in pregnant women has not been established. No controlled clinical trials with lovastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to lovastatin or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking lovastatin or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with lovastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of

lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, lovastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with lovastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3). Lovastatin should only be administered to woman of child bearing potential using highly effective measures of contraception.

Breastfeeding
It is not known whether lovastatin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious side effects, women taking lovastatin should not nurse their infants (see section 4.3).

Fertility
Test in animals have shown effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Lovastatin has no or negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported rarely in post-marketing experiences.

4.8 Undesirable effects

Lovastatin is generally well-tolerated; for the most part side effects have been mild and transient in nature.

The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).
Side effects (considered possibly, probably or definitely related to lovastatin) reported in controlled clinical studies:

	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Endocrine disorders			gynaecomastia
Psychiatric disorders		insomnia, sleep disorder	
Nervous system disorders	headache, dizziness	dysgeusia,	
Eye disorders	blurred vision		
Gastrointestinal disorders	flatulence, diarrhoea, constipation, nausea, dyspepsia, abdominal pain[1]	dry mouth, heartburn	pancreatitis, stomatitis
Skin and subcutaneous tissue disorders	rashes	pruritus	
Musculoskeletal and connective tissue disorders	muscle cramps, myalgia		myopathy; rhabdomyolysis which can be associated with acute renal failure secondary to myoglobinuria, myopathy (see section 4.4)
General disorders and administration site conditions		fatigue	oedema

[1]Patients receiving active control agents had a similar or higher incidence of gastrointestinal side effects.

In the 48-week expanded clinical evaluation of lovastatin (EXCEL study) comparing lovastatin to placebo, the adverse experiences reported were similar to those of the initial studies, and the incidence on drug and placebo was not statistically different.
The following additional side effects have been reported since the drug was marketed:

	Rare (≥ 1/10,000 to < 1/1,000)	Not known (cannot be estimated from available data)
Immune system disorders	hypersensitivity syndrome, in which one or more of the following symptoms may be present (anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, leukopenia, eosinophilia, haemolytic anaemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, flushing, chills, dyspnoea and malaise)	
Metabolism and nutrition disorders		anorexia
Psychiatric disorders		psychic disorder including anxiety, depression
Nervous system disorders		paraesthesia, peripheral neuropathy, memory impairment
Gastrointestinal disorders		vomiting
Hepatobiliary disorders		hepatitis, cholestatic jaundice
Skin and subcutaneous tissue disorders		alopecia, toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders		immune-mediated necrotizing myopathy (see section 4.4)
Reproductive system and breast disorders		erectile dysfunction
Investigations	serum transaminase increased (see section 4.4)	alkaline phosphatase increased, bilirubin increased, serum CK levels increased (attributable to the noncardiac fraction of CK, these have usually been mild and transient; marked elevations have been reported rarely, see section 4.4)

The following adverse events have been reported with some statins:
- Nightmares
- Memory loss
- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30kg/m^2, raised triglycerides, history of hypertension).

Paediatric population
Safety and effectiveness of lovastatin (10, 20 & 40 mg daily) in 100 children 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in controlled clinical trials of 48 weeks duration in adolescent boys and 24 weeks duration in girls who were at least one year post-menarche. Doses greater than 40 mg have not been studied in this population.

The safety profile of lovastatin obtained from these limited controlled studies was generally similar to adults; with the exception of a statistically significant reduction in LH levels in the adolescent girls treated with lovastatin. There was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls (see sections 4.4 and 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Until further experience is obtained, no specific treatment of overdosage with lovastatin can be recommended. General measures should be adopted, and liver function should be monitored.

The dialysability of lovastatin and its metabolites in man is not known at present.
Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patient had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5-6 g.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC-code: C10AA02

Lovastatin is a cholesterol level lowering active substance, which has been isolated from *Aspergillus terreus* fungus. Orally administrated lovastatin, which is an inactive lactone, is hydrolysed immediately into the corresponding beta-hydroxy acid. This main metabolite of lovastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyses the conversion of HMG-CoA to mevalonic acid and this conversion is an early and rate-limiting step in the endogenic cholesterol biosynthesis. Clinical studies have shown that through this mode of action lovastatin lowers the levels of LDL- and VLDL cholesterol in plasma. The results of the studies also show that as the result of lovastatin treatment the lipid levels are reduced, from both normal and elevated baseline levels, and that the concentration of apolipoprotein B is reduced. Since each LDL particle contains one molecule of apolipoprotein B and since apolipoprotein B is only present in very small quantities in other lipoproteins, it can be assumed that lovastatin not only causes a reduction in the cholesterol content of LDL but also a quantitative decrease in LDL. The cholesterol-lowering effect of lovastatin seems to be based on the decrease of VLDL, the precursor of LDL. Furthermore, it has been shown that HDL cholesterol increases moderately during lovastatin therapy. Overall, these changes result in a decrease in the ratios of total cholesterol to HDL cholesterol and of LDL cholesterol to HDL cholesterol. At the same time the triglyceride concentration in plasma decreases.

The efficacy of lovastatin in the treatment of coronary sclerosis was investigated in three randomised placebo-controlled clinical studies lasting from 2 to 2.5 years. All patients had coronary sclerosis confirmed by quantitative coronary angiography (QCA). In all, approx. 700 patients participated the studies. Lovastatin at doses 20 to 80 mg/day could be shown to reduce the progression of lesions significantly in patients with coronary sclerosis and to reduce the number of patients in whom new lesions are observed.
In the treatment of primary hypercholesterolaemia, in which diet only has not proven sufficient, lovastatin lowered the amount of total cholesterol and LDL cholesterol in patients with heterozygous familial and nonfamilial hypercholesterolaemia and also in patients with hyperlipidaemia, when hypercholesterolaemia

was the primary reason for the treatment. After the discontinuation of the lovastatin treatment, the level of total cholesterol has been found to increase back to the level found prior to the treatment.
Lovastatin has been used in the treatment of primary hypercholesterolaemia in patients with uncomplicated, balanced juvenile (type 1) or in adult age (type 2) diabetes. The reduction of the lipid levels in serum in these patients has been of the same order as in patients without diabetes. The treatment has not been found to have any negative effect on the glucose balance.

Paediatric population
In a randomised, double-blind, placebo-controlled study, 132 boys, 10-17 years of age with heterozygous familial hypercholesterolaemia (baseline LDL-C 189-500 mg/dl) were randomised to lovastatin (n=67) or placebo (n=65) for 48 weeks. The dosage of lovastatin once daily in the evening was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. Lovastatin significantly decreased the mean baseline total-C by 19.3%, mean LDL-C by 24.2% and mean apolipoprotein B levels by 21%.
Similarly in another randomised, double-blind, placebo-controlled study, 54 girls 10-17 years of age who were at least one year post-menarche with heterozygous familial hypercholesterolaemia (baseline LDL-C 160-400 mg/dl) were randomised to lovastatin (n=35) or placebo (n=19) for 24 weeks. The dosage of lovastatin once daily in the evening was 20 mg for the first 4 weeks, and 40 mg thereafter. Lovastatin significantly decreased the mean baseline total-C by 22.4%, mean LDL-C by 29.2%, mean apolipoprotein B levels by 24.4% and median triglycerides levels by 22.7%.
The safety and efficacy of doses above 40 mg daily have not been studied in children. The long-term efficacy of lovastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Lovastatin is a lactone, which, *in vivo*, is rapidly hydrolysed into the corresponding beta-hydroxy acid, which is an efficient inhibitor of HMG-CoA reductase.
Following oral administration of ^{14}C-labelled lovastatin in healthy volunteers, 10 % of the dose was excreted in the urine and 83 % in the faeces. The quantity excreted in the faeces included both the substance equivalents excreted in the bile and the equivalents of any non-absorbed substance. The peak of the radioactivity (lovastatin and ^{14}C-metabolites) was reached in plasma in 2 hours and it rapidly decreased in to 10 % of the peak level in 24 hours. Animal studies in four different species have revealed that on average 30 % of the oral dose is absorbed in comparison with the same dose given i.v. Animal studies have shown that after oral administration, lovastatin is mainly transferred to the liver, where its concentration is significantly higher than in other tissues. Lovastatin undergoes an extensive first-pass metabolism in the liver, its primary site of action, after which the active substance is excreted in the bile. This extensive first-pass effect limits the amount of the absorbed active substance to the systemic circulation.

Both lovastatin and its beta-hydroxy acid metabolite are bound to plasma protein to over 95 %. Animal studies have shown that lovastatin crosses both the blood-brain barrier and the placental barrier.
The active main metabolites of lovastatin in the human plasma are its beta-hydroxy acid and the 6'-hydroxy, 6'-hydroxymethyl- and 6'exomethylene derivatives of the latter. The peak concentration of both the active inhibitors and inhibitors in total was achieved in 2 to 4 hours after the oral dose. Studies with increasing single doses have revealed that the inhibitory activity in the systemic circulation increases linearly with the dose up to a dose of 120 mg lovastatin. With a once-a-day dosing regimen, steady state plasma concentrations of total inhibitors were reached between the second and third day of the therapy and the steady state concentration was approx. 1.5-fold in comparison with the concentration obtained with a corresponding single dose. When lovastatin was administrated by subjects under fasting conditions, the plasma concentrations of the total inhibitors were on average 2/3 of those measured when lovastatin was administrated in connection with a standardised meal.

The total concentration of the inhibitors in plasma in patients with severe renal insufficiency (creatinine clearance 10 to 30 ml/min) was after a single dose of lovastatin approx. two-fold, in comparison with the concentration obtained in healthy volunteers.

5.3 Preclinical safety data

The repeated administration of lovastatin in high doses led to toxic effects in various animal species, which were attributable to an excessive pharmacological action. The main target organs were the liver and the CNS.

In studies on dogs cataracts occurred in isolated cases after the administration of lovastatin in the high dose range; however, on the basis of AUC levels there seems to be a sufficiently high safety margin in relation to the human therapeutic dose.

No evidence of a genotoxic potential was found in a battery of (in-vitro and in-vivo) genetic toxicology studies.

An increased incidence of tumours was observed after the administration of lovastatin in long-term studies on mice and rat carried out to detect a tumorigenic potential.

Species	Relative exposure (by comparison with the human therapeutic) on the basis of AUC levels	Tumours observed
Rat	2-7	Hepatocellular carcinomas
Mouse	1-2	Papillomas in squamous (non-glandular) epithelium of the gastric mucosa*
Mouse	3-4	Hepatocellular carcinomas and adenomas
Mouse	4	Pulmonary adenomas

* In humans the gastric mucosa consists exclusively of glandular epithelium

The significance of these findings for long-term therapy in humans is still unclear.

In reproduction toxicology studies skeletal malformations occurred in the foetuses after the administration of high dosages (800 mg/kg/day) to rats and mice. In rabbits no malformations were observed in the offspring with dosages of up to 15 mg/kg/day (MTD).
Fertility was impaired in dogs with dosages from 20 mg/kg/day, but a fertility study in rats proved negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

20 mg: Lactose monohydrate
pregelatinised maize starch
butylated hydroxyanisole
patent blue (E131)
maize starch
microcrystalline cellulose
magnesium stearate.

40 mg: Lactose monohydrate
pregelatinised maize starch
butylated hydroxyanisole
quinoline yellow (E104) (contains sodium)

patent blue (E131)
maize starch
microcrystalline cellulose
magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package.
Do not store above 30 °C.

6.5 Nature and contents of container

10, 20, 28, 30, 50, 60, 98 and 100 tablets in aluminium/PVC/PVDC blister foil.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]