SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Medostatin 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Medostatin tablet contains 20 mg lovastatin.

Excipient with known effect: lactose monohydrate.
Each 20 mg tablet contains 146 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.
20mg: Blue, flat, round, scored tablets, with diameter of 8.0 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Severe cases of hypercholesterolaemia where response to dietary measures has been inadequate.

4.2. Posology and method of administration

Posology

Hypercholesterolaemia

The initial dose is generally 20 mg per day, given as a single dose with the evening meal.
It has been shown that single daily doses given with the evening meal are more effective than the same dose given with breakfast, possibly because cholesterol synthesis takes place mainly at night. Patients may be treated with an initial dose of 10 mg lovastatin. Any dosage adjustments should be made at intervals of at least 4 weeks. A maximum of 80 mg should be given daily in a single dose or divided into 2 doses taken with breakfast and the evening meal. Two daily doses would appear to be more effective than one daily dose.

The dosage of lovastatin should be reduced if LDL-cholesterol levels drop below 1.94 mmol/l, or if total serum cholesterol concentrations fall below 3.6 mmol/l.

Concomitant therapy

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

In patients taking cyclosporine, 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)

Coronary atherosclerosis

In the coronary atherosclerosis trials which utilized 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 utilized lovastatin alone, the dose was reduced if total plasma cholesterol decreased to below 2.85 mmol/L or if LDL-cholesterol decreased to below 2.1 mmol/L, respectively.

Elderly patients

In a controlled trial of the treatment of patients in the over-sixty age group, the effects appeared to be identical to those in the remainder of the population and there was no marked increase in frequency of clinical or laboratory adverse findings.

Patients with renal impairment

Since lovastatin does not undergo significant renal excretion, moderate renal insufficiency does not necessitate any dosage reduction.

In patients with severe renal failure (creatinine clearance <30 ml/min) dosages over 20 mg/day should be carefully considered, and, if necessary, should be commenced with caution (see Section 4.4).

Paediatric population

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

Method of administration

The patient should be placed on a standard cholesterol-lowering diet before being given lovastatin. This diet should be continued during treatment with lovastatin. Any cause for secondary hypercholesterolemia should be excluded before initiation of treatment.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active liver disease or unexplained persistantly elevated serum transaminase levels
Cholestatis
Myopathy
Concomitant administration of potent CYP3A4 inhibitors (e.g. mibefradil, ketoconazole, itraconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors, delavirdine, nefazodone and amiodarone) (see section 4.5)
Pregnancy and lactation (cf. also section 4.6 "Pregnancy and lactation").
Alcoholism

4.4. Special warnings and precautions for use

Muscular effects

Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as musclepain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathysometimes 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 reductaseinhibitory activity in plasma.
The prevalence and severity of myopathy will increase if HMG-CoA reductase inhibitors are given in combination with drugs causing myopathy such as fibrates and niacin. Co-administration of lovastatin and gemfibrozil should be avoided due to pharmacokinetic interactions (see section 4.5). The combination of lovastatin with other fibrates or niacin should be restricted to patients with severe combined hyperlipidaemia and a high cardiovascular risk.

The risk of myopathy/rhabdomyolysis is increased by concomitant use of lovastatin with the following:
Potent inhibitors of CYP3A4, e.g., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone, particularly with higher doses of lovastatin (see Sections 4.5 and 5.2).
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 Section 4.5).

Other drugs:
Cyclosporine or danazol particularly with higher doses of lovastatin (see Sections 4.5 and 5.2).
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).

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.
Since there is an obvious connection between the increased plasma concentration of active metabolites of lovastatin and myopathy, patients using immunosuppressants should not be given more than 20 mg a day (see section 4.2). If a noticeable rise in CK levels is detected or if myopathy is diagnosed or suspected, lovastatin therapy should be discontinued.
HMG-CoA inhibitors and antifungal medicinal products, which are azole derivatives, inhibit cholesterol synthesis at different points in the synthesis chain. Patients who are receiving cyclosporin treatment should have lovastatin therapy withdrawn if systemic fungicide treatment with an azole derivative is necessary. Patients who are not receiving cyclosporin treatment should be carefully monitored if systemic fungicide treatment with an azole derivative is necessary.
Lovastatin treatment must be temporarily interrupted or withdrawn in patients who have a condition which predisposes them to the development of renal failure, such as a serious acute infection, hypotension, major surgery, trauma, a severe metabolic, endocrine or electrolyte balance disorder or uncontrolled epilepsy.
The patient must be encouraged to report without delay if he has unexplained muscular pain, -tenderness or -weakness, particularly if this is associated with general indisposition or fever.
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 value interpretation difficult. If CK levels are significantly elevated at baseline (> 5xULN), 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.

Whilst on treatment

If muscular 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 to be significantly elevated (>5xULN), treatment should be stopped.

If muscular symptoms are severe and cause daily discomfort, even if CK levels are elevated to ≤5xULN, treatment discontinuation should be considered.

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, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone) should be avoided. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin, or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment.

Concomitant use with other medicines labeled 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 (≥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. 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.

4. Lovastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment.

5. 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.

6. 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.

<u>Hepatic impairment</u>

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 (see section 5.1).

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 is a contraindication to the use of Holetar (see section 4.3).

Ophthalmological examinations

The occurrence of lens opacities due to ageing may increase without any medicinal product treatment. The results of long-term clinical trials do not indicate that lovastatin has a harmful effect upon the lens in man.

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>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Pediatric 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.

Elderly

In one controlled study in elderly patients over the age of 60, 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.

Homozygotic familial hypercholesterolaemia

Lovastatin is not as effective as otherwise for patients who are suffering from rare homozygotic familial hypercholesteraemia. This may be due to the fact that these patients do not have functional LDL-receptors. Lovastatin appears more likely than usual to raise the serum transaminase levels in these homozygotic patients.

Hypertriglyceridaemia

Lovastatin lowers the triglyceride concentration only moderately, so that its use is not indicated in cases where hypertriglyceridaemia is the principal therapeutic indication (in hyperlipidaemia types I, IV and V).

Vitamin K antagonists

There is a risk for increased effect of vitamin K antagonists (see section 4.5, sub-section coumarin derivatives).

Impaired renal function

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

Secondary hypercholesterolemia

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

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.

Medostatin contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Gemfibrozil and other fibrates, niacin (nicotinic acid) at lipid-lowering doses (1 g/day). These medicinal products increase the risk of myopathy when they are used in combination with lovastatin (see section 4.4 Special warnings and special precautions for use/Muscular effects).
Co-administration of lovastatin and gemfibrozil led to a considerable increase in the concentration of the active metabolite in plasma in healthy volunteers compared with co-administration of lovastatin and placebo.

Interactions associated with cytochrome P450 3A4
Lovastatin has no inhibitory effect on cytochrome P450 3A4. Therefore, lovastatin is not expected to influence the plasma concentrations of medicinal products metabolized via P450 3A4 cytochrome. However, lovastatin is a substrate of cytochrome P450 3A4. Potent inhibitors of cytochrome P450 3A4 may increase the risk of myopathy by increasing the inhibitory activity HMG-CoA reductase in plasma during lovastatin therapy. Such inhibitors include e.g. ciclosporine, mibefradil, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, verapamil and nefazodone (see section 4.4 Special warnings and special precautions for use/Muscular effects).

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: gemfibrozil and other fibrates, niacin (nicotinic acid) (≥1 g/day).

Other drug interactions
Cyclosporine or Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of lovastatin (see section 4.4, 5.1 and 5.2).

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).
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.
Grapefruit juice contains one or more ingredients that inhibit cytochrome P450 3A4 and may therefore increase the plasma concentrations of medicinal products metabolized via cytochrome P450 3A4. Very high quantities of grapefruit juice (more than a litre a day) significantly increase the inhibitory activity of HMG-CoA reductase during lovastatin therapy and such quantities should therefore be avoided.

Coumarin derivatives
When lovastatin and coumarin derivatives are used concurrently, prothrombin time may be prolonged in some patients. In patients receiving anticoagulant therapy, prothrombin time should be determined before starting lovastatin therapy and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, it can be determined at the intervals usually recommended for patients receiving coumarin therapy. If the dose of lovastatin is changed, the same procedures should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not receiving anticoagulant therapy.

4.6. Fertility, pregnancy and lactation.

Pregnancy
Pregnancy is a contraindication for treatment with lovastatin.
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 fetal 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 hypercholesterolemia. For these reasons, Holetar should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with Holetar should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See section 4.3.)
Isolated cases of congenital abnormalities have been reported in children where the mother was being treated with HMG-CoA reductase inhibitors during pregnancy (cf. section 4.3). In a trial which followed 100 pregnant women who had been exposed to lovastatin or other structurally related HMG-CoA reductase inhibitors, the incidence of congenital abnormalities, spontaneous abortions and foetal mortality/stillbirth was no higher than would have been expected in the general population. Since safety has not been investigated in pregnant women and since there is no special advantage in treatment with lovastatin during pregnancy, treatment should be discontinued immediately as soon as pregnancy is established.

Breast-feeding
It is not known whether lovastatin is excreted in breastmilk. However, since many drugs are excreted in breastmilk and since there is a potential risk of serious side effects, women taking lovastatin should not breast-feed their babies.

Fertility
No human fertility data are available.

4.7. Effects on the 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 postmarketing experiences.

4.8. Undesirable effects

- 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)

Summary of the safety profile

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

In controlled clinical studies, side effects (considered possibly, probably or definitely drug related) occurring with a frequency of greater than 1% were: flatulence, diarrhea, constipation, nausea, dyspepsia, dizziness, blurred vision, headache, muscle cramps, myalgia, rashes, and abdominal pain. Patients receiving active control agents had a similar or higher incidence of gastrointestinal side effects. Other side effects occurring in 0.5 to 1.0% of patients were: fatigue, pruritus, dry mouth, insomnia, sleep disorders, and dysgeusia.

Uncommon adverse reactions were tiredness, pruritus, xerostomia, insomnia, sleeping difficulties and dysgeusia.

Rare adverse reactions were myopathy, rhabdomyolysis and peripheral polyneuropathy (in particular if used for long period of time).In rare cases erectile dysfunction occurred in conjunction with HMG-CoA-reductase inhibitors.

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: hepatitis, cholestatic jaundice, vomiting, anorexia, paresthesia, peripheral neuropathy, memory impairment, psychic disturbances including anxiety, depression, erectile dysfunction, alopecia, toxic epidermal necrolysis and erythema multiforme, including Stevens-Johnson syndrome.

Manifest hypersensitivity syndrome has been reported in rare instances. It has been associated with one or more of the following symptoms: anaphylaxis, angioneurotic oedema, lupus-like syndrome, polymyalgia rheumatics, vasculitis, thrombocytopenia, leukopenia, eosinophilia, haemolytic anaemia, positive antinuclear antibodies, increased sedimentation rate, arthritis and arthralgia, urticaria, asthenia, photosensitivity, fever, flushing, shivering, shortness of breath and indisposition.

The following other adverse reactions are reported to have occurred after the product came into clinical use: hepatitis, cholestatic jaundice, vomiting, anorexia, paraesthesiae, peripheral neuropathy and psychological disorders such as anxiety, alopecia, toxic epidermal necrolysis and erythema multiforme, also Stevens-Johnson syndrome, immune-mediated necrotizing myopathy (see section 4.4).

The following adverse events have been reported with some statins:

- Sleep disturbances, including nightmares
- Memory loss
- Sexual dysfunction
- Depression
- 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/m2, raised triglycerides, history of hypertension)

Laboratory findings

A noticeable and long-term rise in the serum transaminase level has been reported as a rare finding (0.01-0.1 %) (see section 4.4 Special warnings and special precautions for use). Other reported abnormalities of liver function tests have been increased alkaline phosphatase and bilirubin. A rise in the creatine kinase level due to a CK fraction of non-cardiac origin has been observed. In most cases the rise has been mild and transient; a considerable increase has been reported only in rare instances (see section 4.4 Special warnings and special precautions for use/Muscular effects).

Paediatric population

Safety and effectiveness of lovastatin (10, 20 & 40 mg daily) in 100 children 10-17 years of age with heterozygous familial hypercholesterolemia 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 is an important way to gather more information to continuously monitor the benefit / risk balance of the medicinal product. Any suspected adverse reactions should be reported via the national reporting system.

4.9. Overdose

No specific treatment can be recommended until further experience with overdose of lovastatin has been obtained. Normal measures should be adopted and liver function monitored.
The capacity of lovastatin and its metabolite for dialysis is not yet known.

Five healthy volunteers were given up to 200 mg lovastatin as a single dose without clinically significant side effects. Isolated cases of accidental overdose have been reported. None of the patients had specific symptoms and all recovered without sequelae. The highest dose was 5 to 6 g.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Lovastatin, an inactive lactone, is hydrolysed to the corresponding hydroxy acid after oral administration. This acid inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme which catalyses an early and rate-limiting step in the biosynthesis of cholesterol. In clinical trials, lovastatin reduced serum concentrations of total cholesterol and of LDL- and VLDL-cholesterol (low-density and very low-density lipoprotein). Lovastatin also caused a moderate increase in HDLcholesterol (high-density lipoprotein) and reduced plasma triglycerides. The active form of lovastatin is a specific inhibitor of HMG-oA reductase, the enzyme which catalyses the conversion of HMGCoA to mevalonate. Since the conversion of HMG-CoA to mevalonate is an early stage in the biosynthesis of cholesterol, treatment with Lovastatin is not thought to cause accumulation of any toxic sterols. Moreover, HMG-CoA is itself rapidly converted to acetyl-CoA which is part of many biosynthesis processes in the body.

Paediatric population

In a randomized, double-blind, placebo-controlled study, 132 boys, 10-17 years of age with heterozygous familial hypercholesterolemia (baseline LDL-C 189-500 mg/dL) were randomized 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 randomized, double-blind, placebo-controlled study, 54 girls 10-17 years of age who were at least one year post-menarche with heterozygous familial hypercholesterolemia (baseline LDL-C 160-400 mg/dL) were randomized 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

In animal experiments (oral administration), lovastatin exhibited high liver selectivity, with far higher concentrations being found there than in other tissue. lovastatin undergoes extensive first-pass extraction in the liver, the primary site of action of the substance, with subsequent excretion in the bile. After oral administration of lovastatin to test subjects, 10% of the dose was excreted in urine and 83% in the faeces. Both lovastatin and its beta-hydroxy acid bind to human plasma proteins (> 95%). Animal studies have shown that lovastatin penetrates the blood/brain barrier and the placenta barrier. The peak plasma concentration of lovastatin and its active metabolite is reached over 2 to 4 hours after administration. Plasma concentrations are linear up to a dose of 120 mg lovastatin. On daily administration, "steady state" plasma concentrations are reached between the 2nd and 3rd day. On administration in a fasting state, the concentration of lovastatin and the active metabolite reached corresponds to 2/3 of the plasma concentration on administration immediately after a normal meal.

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

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

Lactose monohydrate, starch maize pregelatinised, cellulose microcrystalline, butylated hydroxy anisole (BHA), magnesium stearate.
Medostatin 20mg tablets contain also indigotine blue aluminum lake (E132).

6.2. Incompatibilities

None.

6.3. Shelf life

36 months

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions

6.5. Nature and contents of container

Medostatin 20 mg tablets: PVC-Al blisters. Each blister contains 10 tablets. Boxes containing 20, 30 or 50 tablets are available.

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBERS

08353/08601/REN/2022

9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26/06/2003
Date of latest renewal: 03/01/2023

10. DATE OF REVISION OF THE TEXT

07/2023