

Name of Medicine

LIPEX[®]

simvastatin

10 mg, 20 mg, 40 mg, 80 mg tablets

Presentation

LIPEX 10 mg is a peach coloured oval shaped biconvex film coated tablet imprinted MSD735 on one side and unmarked on the other. Dimensions 8.51 mm x 5.05 mm.

LIPEX 20 mg is a tan coloured oval shaped biconvex film coated tablet imprinted MSD740 on one side and unmarked on the other. Dimensions 11.10 mm x 6.35 mm.

LIPEX 40 mg is a brick red oval shaped biconvex film coated tablet imprinted MSD749 on one side and unmarked on the other. Dimensions 8 mm x 14 mm.

LIPEX 80 mg is a brick red capsule shaped tablet imprinted 543 on one side and 80 on the other. Dimensions 17.46 mm x 7.5 mm.

Therapeutic Class

LIPEX (simvastatin, MSD) is a lipid lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*.

Indications

Patients at High Risk of Coronary Heart Disease (CHD) or With Existing CHD

In patients at high risk of CHD (with or without hyperlipidaemia but with a total cholesterol of >3.5 mmol/L), ie., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD, LIPEX is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths;
- Reduce the risk of major vascular events (a composite of non-fatal myocardial infarction, CHD death, stroke, or revascularisation procedures);
- Reduce the risk of major coronary events (a composite of non-fatal myocardial infarction or CHD deaths);
- Reduce the risk of stroke;
- Reduce the need for coronary revascularisation procedures (including coronary artery bypass grafting and percutaneous transluminal coronary angioplasty);
- Reduce the need for peripheral and other non-coronary revascularisation procedures;
- Reduce the risk of hospitalisation for angina pectoris.

In patients with diabetes, LIPEX reduces the risk of developing peripheral macrovascular complications (a composite of peripheral revascularisation procedures, lower limb amputations, or leg ulcers).

In hypercholesterolaemic patients with coronary heart disease, LIPEX slows the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions.

Patients With Hyperlipidaemia

- LIPEX is indicated as an adjunct to diet to reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), triglycerides TG, and, apolipoprotein B (apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolaemia including heterozygous familial hypercholesterolaemia (Fredrickson type IIa), or combined (mixed) hyperlipidaemia (Fredrickson type IIb) when response to diet and other non-pharmacological measures is inadequate. LIPEX therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios.
- LIPEX is indicated for the treatment of patients with hypertriglyceridaemia (Fredrickson type IV hyperlipidaemia) with a baseline LDL cholesterol of <3.37 mmol/L and baseline triglyceride of >2.26 mmol/L, despite adequate dietary intervention.
- LIPEX is indicated for the treatment of patients with primary dysbetalipoproteinaemia (Fredrickson type III hyperlipidaemia) not responding to diet alone with VLDL/TG ratios >0.25, and raised total cholesterol, TG and Apo-E levels.
- LIPEX is also indicated as an adjunct to diet and other non-dietary measures for the treatment of patients with homozygous familial hypercholesterolaemia to reduce elevated total-C, LDL-C and apoB.

Paediatric Patients with Heterozygous Familial Hypercholesterolaemia

- LIPEX is indicated as an adjunct to diet to reduce total-C, LDL-C, TG, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolaemia (HeFH).

Dosage and Administration

The dosage range for LIPEX is 5-80 mg/day, given as a single dose in the evening. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg/day given as a single dose in the evening. The 80 mg dose of LIPEX is only recommended in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks (see Warning and Precautions, *Myopathy/Rhabdomyolysis*).

LIPEX may be taken with or without food.

Patients at High Risk of Coronary Heart Disease (CHD) or With Existing CHD

The usual starting dose of LIPEX is 40 mg/day given as a single dose in the evening in patients at high risk of CHD (with or without hyperlipidaemia) ie., patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD. Medicine therapy can be initiated simultaneously with diet and exercise.

Patients With Hyperlipidaemia (Who Are Not in The Risk Categories Above)

The patient should be placed on a standard cholesterol-lowering diet before receiving LIPEX and should continue on this diet during treatment with LIPEX.

The usual starting dose is 20 mg/day given as a single dose in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg/day given as a single dose in the evening. Patients who require only a moderate reduction of LDL-C may be started at 10 mg. Adjustments of dosage including starting dose, if required, should be made as specified above.

Patients With Homozygous Familial Hypercholesterolaemia

Based on results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolaemia is LIPEX 40 mg/day in the evening or 80 mg/day in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg. The 80mg dose is only recommended when the benefits are expected to outweigh the potential risks (see Contraindications; Warning and Precautions, *Myopathy/Rhabdomyolysis*). LIPEX should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Concomitant Therapy

LIPEX is effective alone or in combination with bile acid sequestrants.

In patients taking amiodarone, verapamil, diltiazem or ≥ 1 g/day of niacin concomitantly with LIPEX, the dose of LIPEX should not exceed 20 mg/day. (See Warnings and Precautions, *Myopathy/Rhabdomyolysis* and Interactions.)

In patients taking amlodipine concomitantly with LIPEX, the dose of LIPEX should not exceed 40 mg/day. (See Warnings and Precautions, *Myopathy/Rhabdomyolysis* and Interactions.)

Dosage In Renal Insufficiency

Because LIPEX 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 10 mg/day should be carefully considered and, if deemed necessary, implemented cautiously.

Dosage in Paediatric Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolaemia

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualised according to the recommended goal of therapy (see Actions).

Contraindications

- Hypersensitivity to any component of this preparation.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing (see also Warnings and Precautions, *Pregnancy and Nursing Mothers*).
- Myopathy secondary to other lipid lowering agents.
- Concomitant administration of potent CYP3A4 inhibitors (eg. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*).
- Concomitant administration of gemfibrozil, cyclosporin, or danazol (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

Warnings and Precautions

Myopathy/Rhabdomyolysis

Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X 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. Predisposing factors for myopathy include advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,413 patients were treated with LIPEX, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial (SEARCH) in which patients with a history of myocardial infarction were treated with LIPEX 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. This includes rhabdomyolysis for which the incidence was 0.1 to 0.2%, all allocated to simvastatin 80 mg/day. There is no universally accepted definition of rhabdomyolysis. In SEARCH, rhabdomyolysis was defined as a subset of myopathy with CK $> 40 \times$ ULN plus evidence of end organ damage (e.g. elevated creatinine, dark urine). Approximately half of these myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%.

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C lowering efficacy. Therefore the 80 mg dose of LIPEX should only be used in patients at high risk for cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks. In patients taking LIPEX 80 mg for whom an interacting agent is needed, a lower dose of LIPEX or an alternative statin-ezetimibe regimen with less potential for drug-drug interactions should be used (see Contraindications; Dosage and Administrations).

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and 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 simvastatin or whose dose is being increased. Periodic CK determinations are recommended for patients titrating to the 80 mg dose. There is no assurance that such monitoring will prevent myopathy.

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

Drug Interactions

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

Contraindicated medicines

Potent inhibitors of CYP3A4: Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses eg., itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone, is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin is unavoidable, therapy with LIPEX should be suspended during the course of treatment (see Contraindications, Interactions, *CYP3A4 Interactions*, and Pharmacokinetics).

Gemfibrozil, cyclosporine or danazol: Concomitant use of these drugs with LIPEX is contraindicated, (see Contraindications, Interactions, and Pharmacokinetics).

Other Medicines

Amiodarone In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. The dose of LIPEX should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone (See Dosage and Administrations, Interactions)

Calcium channel blockers

Verapamil or diltiazem: In a pharmacokinetic study, co-administration of diltiazem and simvastatin resulted in a mean 70% increase in systemic exposure to total simvastatin-derived HMG-CoA reductase inhibitory activity. In a clinical trial, patients on diltiazem treated concomitantly with simvastatin 80 mg had an increased risk of myopathy. The dose of LIPEX should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem (see Dosage and Administrations; Interactions).

Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The dose of LIPEX should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine (see Dosage and Administrations, Interactions).

Moderate inhibitors of CYP3A4: Patients taking other medicines labelled as having a moderate inhibitor effect on CYP3A4 concomitantly with LIPEX, particularly higher LIPEX doses, may have an increased risk of myopathy.

Other Fibrates: The safety and effectiveness of LIPEX administered with fibrates have not been studied. Therefore, the concomitant use of LIPEX and fibrates should be avoided. Concomitant use of gemfibrozil is contraindicated (see Contraindications; Interactions with other medicines).

Fusidic acid: Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy. Patients on fusidic acid and LIPEX should be closely monitored. Temporary suspension of LIPEX treatment may be considered. (see Interactions, *Other medicine interactions*, and Pharmacokinetics).

Niacin (≥1 g/day): The dose of LIPEX should not exceed 20 mg daily in patients

receiving concomitant medication with niacin (nicotinic acid) ≥ 1 g/day. Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid modifying doses (≥ 1 g/day) of niacin. In an ongoing, double-blind, randomised cardiovascular outcomes trial conducted in China, the United Kingdom and Scandinavia, an interim analysis by the independent safety monitoring committee revealed that the incidence of myopathy among approximately 4700 UK/Scandinavian patients treated with either simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg coadministered with extended-release (ER) niacin/laropiprant 2 g/40 mg is similar to the overall incidence reported in the clinical trial database for simvastatin 40 mg (0.08%). However, in approximately 3900 Chinese patients in the same treatment arm, the incidence is higher than expected (approximately 0.9%). The risk of myopathy was not increased among 8600 Chinese, UK, or Scandinavian patients in the control arm (placebo plus simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg). Because the incidence of myopathy is higher in Chinese than in non-Chinese patients, caution should be used when treating Chinese patients with simvastatin (particularly doses of 40 mg or higher) co-administered with lipid modifying doses (≥ 1 g/day) of niacin or niacin-containing products. Because the risk of myopathy is dose-related, the use of simvastatin 80 mg with lipid modifying doses (≥ 1 g/day) of niacin or niacin-containing products is not recommended in Chinese patients. It is unknown whether there is an increased risk of myopathy with coadministration in other Asian patients. see Interactions, *Other medicine interactions*.

Hepatic Effects

It is recommended that liver function tests (LFT) be performed before treatment begins and thereafter when clinically indicated. Patients titrated to the 80 mg dose should receive an additional test prior to titration, 3 months after titration to the 80 mg dose, and periodically thereafter (e.g., semi-annually) for the first year of treatment. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3X ULN and are persistent, the medicine should be discontinued. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see Warnings and Precautions, *Myopathy/ Rhabdomyolysis*).

In clinical studies persistent increases (to more than 3X ULN) in serum transaminases have occurred in a few adult patients who received simvastatin. When the medicine was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pre-treatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. Some of these patients had abnormal LFT prior to therapy with simvastatin and/or consumed substantial quantities of alcohol.

In the 4S, the number of patients with more than one transaminase elevation to $>3X$ ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). The frequency of single elevations of SGPT (ALT) to 3X ULN was significantly higher in the simvastatin group in the first year of the study (20 vs. 8, $p=0.023$), but not thereafter. Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group ($n=2,221$) and 5 in the placebo group ($n=2,223$). Of the 1986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to $>3X$ ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1105 patients, the 6 month incidence of persistent hepatic transaminase elevations considered medicine-related was 0.7% and 1.8% at the 40 and 80 mg dose respectively.

In the Heart Protection Study, in which 20, 536 patients were randomised to receive LIPEX 40 mg/day or placebo, the incidences of elevated transaminases (>3X ULN confirmed by repeat test) were 0.21% (n = 21) for patients treated with LIPEX and 0.09% (n = 9) for patients treated with placebo.

The medicine should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Ophthalmic Evaluations

In the absence of any medicine therapy, there is generally an increase in the prevalence of lens opacities with time as a result of ageing. Current long term data from clinical studies do not indicate an adverse effect of simvastatin on the human lens.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. 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.

Pregnancy

LIPEX is contraindicated during pregnancy.

Safety in pregnant women has not been established. No controlled clinical trials with simvastatin 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 LIPEX 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 LIPEX or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with LIPEX 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 medicines during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, LIPEX should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with LIPEX should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See Contraindications.)

Nursing Mothers

It is not known whether simvastatin or its metabolites are excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions, women taking LIPEX should not breast feed their infants (see Contraindications).

Paediatric Use

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolaemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least one year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. (See Dosage and Administration, Adverse Effects, Actions.) Adolescent females should be counselled on appropriate contraceptive methods while on simvastatin therapy (Contraindications; Warnings and Precautions, *Pregnancy*). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

Elderly

For patients over the age of 65 years who received simvastatin in controlled clinical studies, efficacy, as assessed by reduction in total and LDL-C levels, appears similar to that seen in the population as a whole, and there is no apparent increase in the overall frequency of clinical or laboratory adverse findings. However, in a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥ 65 years of age had an increased risk of myopathy compared to patients < 65 years of age.

Animal Toxicology

Reproductive and Developmental Toxicity

At maximally tolerated doses in both the rat and the rabbit, simvastatin produced no foetal malformations and had no effects on fertility, reproductive function or neonatal development. However, in rats, an oral dose of 60 mg/kg/day of the hydroxy acid, pharmacologically active metabolite of simvastatin resulted in decreased maternal body weight and an increased incidence of foetal resorptions and skeletal malformations compared with controls. Subsequent studies conducted at dosages of up to 60 mg/kg/day with this metabolite showed that these resorptions and skeletal malformations were consequences of maternal toxicity (forestomach lesions associated with maternal weight loss) specific to rodents and are highly unlikely to be due to a direct effect on the developing foetus. Although no studies have been conducted with simvastatin, maternal treatment of pregnant rats with a closely related HMG-CoA reductase inhibitor at dosages of 80 and 400 mg/kg/day (10- and 52-fold the maximum recommended therapeutic dose based on mg/m² body surface area) has been shown to reduce the foetal plasma levels of mevalonate.

Genetic Toxicology and Carcinogenicity

An extensive battery of *in vitro* and *in vivo* genetic toxicity tests have been conducted on both simvastatin and its corresponding open acid L-654,969. These include assays for microbial mutagenesis, mammalian cell mutagenesis, single stranded DNA breakage and tests for chromosome aberrations. The results of these studies provided no evidence of an interaction between simvastatin or L-654,969 with genetic material at the highest soluble noncytotoxic concentrations tested in *in vitro* assay systems or at maximally tolerated doses tested *in vivo*.

Initial carcinogenicity studies conducted in rats and mice with simvastatin employed doses ranging from 1 mg/kg/day to 25 mg/kg/day. No evidence of a treatment-related incidence of tumour types was found in mice in any tissue. A statistically significant ($p \leq 0.05$) increase in the incidence of thyroid follicular cell adenomas was observed in female rats receiving 25 mg/kg of simvastatin per day (more than an order of magnitude greater than the maximum human dose). This benign tumour type was limited to female rats; no similar changes were seen in male rats or in female rats at lower dosages (up to 5 mg/kg/day). These tumours are a secondary effect reflective of a simvastatin-mediated enhancement of thyroid hormone clearance in the female rat. No other statistically significant increased evidence of tumour types was identified in any tissues in rats receiving simvastatin.

Data from both of these studies indicated that squamous epithelial hyperplasia of the forestomach occurred at all dosage levels. These gastric changes are confined to an anatomical structure which is not found in humans. Moreover, identical cells found in other locations (e.g. oesophagus and anorectal junction of the rat, mouse and dog) are unaffected.

Results of an additional 73-week carcinogenicity study in mice receiving simvastatin doses up to 400 mg/kg/day (more than 2 orders of magnitude greater than the maximum human dose) exhibited increased incidences of hepatocellular adenomas and carcinomas, pulmonary adenomas and harderian gland adenomas. A no-effect dose of 25 mg/kg/day (again, more than an order of magnitude greater than the maximum human dose) was established in this study and from the results of the initial 92-week carcinogenicity study in mice.

Results of an additional 106-week carcinogenicity study in rats receiving simvastatin doses ranging from 50 mg/kg/day to 100 mg/kg/day (more than an order of magnitude greater than the maximum human dose) exhibited a treatment-related increase in the incidence of hepatocellular neoplasms. The no-effect dose remains at 25 mg/kg/day (more than an order of magnitude greater than the maximum human dose) as established in the initial carcinogenicity study. An increase in the incidence of thyroid hyperplastic lesions was also observed; however, this is consistent with the previous finding that this is a species-specific response and has no implications for man.

Effects on Ability to Use and Drive Machinery

LIPEX is presumed to be safe and unlikely to produce an effect on the ability to drive or use machinery.

Adverse Effects

LIPEX is generally well-tolerated; for the most part adverse effects have been mild and transient in nature. Less than 2 percent of patients were discontinued from controlled clinical studies due to adverse effects attributable to LIPEX.

In the pre-marketing controlled clinical studies, adverse effects occurring with a frequency of 1 percent or more and considered by the investigator as possibly, probably or definitely medicine-related were: abdominal pain, constipation and flatulence. Other adverse effects occurring in 0.5 - 0.9 percent of patients were asthenia, headache, and acid regurgitation.

Myopathy has been reported rarely.

In the Heart Protection Study involving 20, 536 patients treated with 40 mg/day of LIPEX (n = 10,269) or placebo (n = 10,267), the safety profiles were comparable between patients treated with LIPEX and patients treated with placebo over the mean 5 years of the

study. In this mega-trial, only serious adverse effects and discontinuations due to any adverse effects were recorded. Discontinuation rates due to adverse effects were comparable (4.8% in patients treated with LIPEX compared with 5.1% in patients treated with placebo). The incidence of myopathy was < 0.1% in patients treated with LIPEX. Elevated transaminases (>3X ULN confirmed by repeat test) occurred in 0.21% (n = 21) of patients treated with LIPEX compared with 0.09% (n = 9) of patients treated with placebo.

In 4S, involving 4,444 patients treated with 20-40 mg/day of LIPEX (n=2,221) or placebo (n=2,223), the safety and tolerability profiles were comparable between treatment groups over the median 5.4 years of the study.

The following additional adverse effects were reported either in uncontrolled clinical studies or in marketed use: nausea, diarrhoea, rash, dyspepsia, pruritis, alopecia, dizziness, muscle cramps, myalgia, pancreatitis, paresthesia, peripheral neuropathy, memory impairment, insomnia, depression, vomiting, gynaecomastia, anaemia, erectile dysfunction, and interstitial lung disease. Rarely rhabdomyolysis and hepatitis/jaundice, and very rarely hepatic failure have occurred. An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopaenia, eosinophilia, ESR increased, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea and malaise.

The following adverse events have been reported with some statins:

- sleep disturbances, including insomnia and nightmares
- memory loss
- sexual dysfunction
- depression
- exceptional cases of interstitial lung disease, especially with long term therapy

Another reported adverse effect not considered to be medicine related was chest pain.

Laboratory Test Findings

Marked and persistent increases of serum transaminases have been reported infrequently. Elevated alkaline phosphatase and γ -glutamyl transpeptidase have been reported. Liver function test abnormalities have generally been mild and transient. Increases in CK levels, derived from skeletal muscle, have been reported (see Warnings and Precautions).

Paediatric Patients (Ages 10-17 years)

In a study involving paediatric patients 10-17 years of age with heterozygous familial hypercholesterolaemia (n = 175), the safety and tolerability profile of the group treated with LIPEX was generally similar to that of the group treated with placebo (see Warnings and Precautions, *Paediatric Use*, and Actions).

Adverse Effects - Causal Relationship Unknown

The following adverse effects have been reported; however, a causal relationship to therapy with LIPEX has not been established: erythema multiforme including Stevens-Johnson syndrome, leukopaenia, proteinuria, and purpura.

Interactions

Contraindicated medicines

Concomitant use of the following medicines is contraindicated:

Potent Inhibitors of CYP3A4

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of simvastatin.

Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 (eg. itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone) is contraindicated. (see Contraindications, Warnings and Precautions, *Myopathy/Rhabdomyolysis, Interactions*).

Gemfibrozil, cyclosporine or danazol: (see Contraindications; Warnings and Precautions, *Myopathy/Rhabdomyolysis, Interactions*).

Other medicine interactions

Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin (see Dosage and Administration, Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

Calcium channel blockers: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine (see Dosage and Administrations; Warnings and Precautions, *Myopathy/Rhabdomyolysis, Interactions*).

Moderate inhibitors of CYP3A4: Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with LIPEX, particularly higher LIPEX doses, may have an increased risk of myopathy.*

Niacin (nicotinic acid) (≥ 1 g/day): Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid modifying doses (≥ 1 g/day) of niacin (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

Fusidic Acid: Patients on fusidic acid treated concomitantly with simvastatin may have an increased risk of myopathy (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*, and Pharmacokinetics).

Colchicine: There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Close clinical monitoring of such patients taking this combination is advised.

Grapefruit juice: contains one or more components that inhibit CYP3A4 and can increase the plasma levels of medicines metabolised by CYP3A4. The effect of typical consumption (one 250-mL glass daily) is minimal (13% 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 litre daily) significantly increase the plasma levels of HMG-CoA reductase inhibitory activity during simvastatin therapy and should be avoided (see Warnings and Precautions, *Myopathy/Rhabdomyolysis*).

Coumarin Derivatives

In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20–40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting simvastatin 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 the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Medicine interaction studies were performed with the following compounds.

Propranolol

In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of LIPEX and propranolol.

Digoxin

Concomitant administration of LIPEX and digoxin in normal volunteers resulted in a slight elevation (less than 0.3 ng/mL) in medicine concentrations (as measured by a digoxin radioimmunoassay) in plasma compared to concomitant administration of placebo and digoxin.

Other Concomitant Therapy

In clinical studies, LIPEX was used concomitantly with angiotensin converting enzyme (ACE) inhibitors, beta blockers, diuretics and nonsteroidal anti-inflammatory medicines (NSAIDs) without evidence of clinically significant adverse interactions.

Overdosage

A few cases of overdosage have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. General measures should be adopted.

Actions

LIPEX (simvastatin, MSD) is a lipid-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*.

After oral ingestion, LIPEX, an inactive lactone, is hydrolysed to the corresponding β -hydroxyacid form. This is a principal metabolite and an inhibitor of HMG-CoA reductase, the enzyme that catalyses an early and rate-limiting step in the biosynthesis of cholesterol. Clinical studies show LIPEX to be highly effective in reducing total-C, LDL-C, TG, and very-low-density lipoprotein cholesterol VLDL-C concentrations, and increasing HDL-C in heterozygous familial and non-familial forms of hypercholesterolaemia, and in mixed hyperlipidaemia when elevated cholesterol was cause for concern and diet alone has been insufficient. Marked responses are seen within 2 weeks, and maximum therapeutic responses occur within 4–6 weeks. The response is maintained during continuation of therapy. When therapy with LIPEX is stopped, cholesterol and lipids return to pre-treatment levels.

The active form of simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyses the conversion of HMG-CoA to mevalonate. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway of cholesterol, therapy with LIPEX would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is also metabolised readily back to acetyl-CoA, which participates in many biosynthetic processes in the body.

In animal studies, after oral dosing, simvastatin had high selectivity for the liver, where it achieved substantially higher concentrations than in non-target tissues. Simvastatin undergoes extensive first-pass extraction in the liver, the primary site of action, with subsequent excretion of medicine in the bile. Systemic exposure of the active form of simvastatin in humans has been found to be less than 5% of the oral dose. Of this, 95% is bound to human plasma proteins.

LIPEX raises HDL-C and therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios.

Clinical Studies

In the Scandinavian Simvastatin Survival Study (4S), the effect on total mortality of therapy with LIPEX for a median of 5.4 years was assessed in 4,444 patients with coronary heart disease (CHD) and baseline total-C 212-309 mg/dL (5.5-8.0 mmol/L). In this multicentre, randomised, double-blind, placebo-controlled study, LIPEX reduced the risk of death by 30%, of CHD death by 42%, and of having a hospital-verified nonfatal myocardial infarction by 37%. LIPEX reduced the risk for undergoing myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37%. In patients with diabetes mellitus the risk of a major coronary event was reduced by 55%. Furthermore, LIPEX significantly reduced the risk of fatal plus nonfatal cerebrovascular events (stroke and transient ischaemic attacks) by 28%.

In the Heart Protection Study (HPS), the effects of therapy with LIPEX for a mean duration of 5 years were assessed in 20,536 patients, with or without hyperlipidaemia, who were at high risk of coronary heart disease (CHD) events because of diabetes, history of stroke or other cerebrovascular disease, peripheral vessel disease, or CHD. At baseline, 33% had LDL levels below 116 mg/dL; 25% had levels between 116 mg/dL and 135 mg/dL; and 42% had levels greater than 135 mg/dL.

In this multicentre, randomised, double-blind, placebo-controlled study, LIPEX 40 mg/day compared with placebo reduced the risk of total mortality by 13%, due to a reduction in CHD deaths (18%). LIPEX also decreased the risk of major coronary events (a composite endpoint comprising non-fatal MI or CHD deaths) by 27%. LIPEX reduced the need for undergoing coronary revascularisation procedures (including coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) and peripheral and other non-coronary revascularisation procedures by 30% and 16%, respectively. LIPEX reduced the risk of stroke by 25%, attributable to a 30% reduction in ischaemic stroke. Furthermore, LIPEX reduced the risk of hospitalisation for angina pectoris by 17%. The risks of major coronary events and major vascular events (a composite endpoint comprising major coronary events, stroke, or revascularisation procedures) were reduced by about 25% in patients with or without CHD, including diabetics and patients with peripheral or cerebrovascular disease. In addition, within the subgroup of patients with diabetes, LIPEX reduced the risk of developing macrovascular complications, including peripheral revascularisation procedures (surgery or angioplasty), lower limb amputations, or leg ulcers by 21%. The risk reductions produced by LIPEX in both major vascular events and major coronary events were evident and consistent regardless of patient age, gender, baseline LDL-C, HDL-C, TG, apolipoprotein A-I, or apolipoprotein B level, presence or absence of hypertension, creatinine levels up to the entry limit of 2.3 mg/dL, presence or

absence of baseline cardiovascular medications (i.e., aspirin, beta blockers, angiotensin converting enzyme (ACE) inhibitors, or calcium channel blockers), smoking status, alcohol intake, or obesity. By 5 years, 32% of patients in the placebo group were taking a statin (outside of the study protocol), so that the observed risk reductions underestimate the real effect of simvastatin.

Clinical Studies in Paediatric Patients (10-17 years of age)

In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (HeFH) were randomised to simvastatin or placebo for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo.

LIPEX significantly decreased plasma levels of total-C, LDL-C, TG, and Apo B. Results from the extension at 48 weeks were comparable to those observed in the base study.

After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the LIPEX 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

LIPEX decreased the mean baseline total-C by 26.5% (placebo: 1.6% increase from baseline), LDL-C by 36.8% (placebo: 1.1% increase from baseline), median TG by 7.9% (placebo: 3.2%), and mean Apo B levels by 32.4% (placebo: 0.5%), and increased mean HDL-C by 8.3% (placebo: 3.6%).

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolaemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

Pharmacokinetics

Simvastatin is an inactive lactone which is readily hydrolysed *in vivo* to the corresponding β -hydroxyacid, L-654,969, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors). Both are measured in plasma following administration of simvastatin.

In a disposition study with ^{14}C -labelled simvastatin, 100 mg (20 μCi) of medicine was administered as capsules (5 x 20 mg), and blood, urine, and faeces collected. Thirteen percent of the radioactivity was recovered in the urine and 60 percent in faeces. The latter represents absorbed medicine equivalents excreted in bile as well as unabsorbed medicine. Less than 0.5 percent of the dose was recovered in urine as HMG-CoA reductase inhibitors. In plasma, the inhibitors account for 14 percent and 28 percent (active and total inhibitors) of the AUC of total radioactivity, indicating that the majority of chemical species present were inactive or weak inhibitors.

Both simvastatin and L-654,969 are bound to human plasma proteins (95%). The major metabolites of simvastatin present in human plasma are L-654,969 and four additional active metabolites. The availability of L-654,969 to the systemic circulation following an oral dose of simvastatin was estimated using an IV reference dose of L-654,969; the value

was found to be less than 5 percent of the dose. By analogy to the dog model, simvastatin is well absorbed and undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of medicine equivalents in the bile. Consequently, availability of active medicine to the general circulation is low.

In dose-proportionality studies utilising doses of simvastatin of 5, 10, 20, 60, 90 and 120 mg there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before a test meal.

The pharmacokinetics of single and multiple doses of simvastatin showed that no accumulation of medicine occurred after multiple dosing. In all of the above pharmacokinetic studies, the maximum plasma concentration of inhibitors occurred 1.3 to 2.4 hours post dose.

In a study of patients with severe renal insufficiency (creatinine clearance <30 mL/min), the plasma concentrations of total inhibitors after a single dose of a related HMG-CoA reductase inhibitor were approximately two-fold higher than those in healthy volunteers.

In a study of 12 healthy volunteers, simvastatin at the maximal 80 mg dose had no effect on the metabolism of the probe CYP3A4 substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4, and therefore, is not expected to affect the plasma levels of other medicines metabolised by CYP3A4.

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

In a pharmacokinetic study, concomitant administration of diltiazem caused a 2.7-fold increase in exposure of simvastatin acid, presumably due to inhibition of CYP3A4.

In a pharmacokinetic study, concomitant administration of amlodipine caused a 1.6-fold increase in exposure of simvastatin acid.

In a pharmacokinetic study, the co-administration of a single dose of niacin extended-release 2 g with simvastatin 20 mg resulted in a modest increase in the AUC of simvastatin and simvastatin acid and in the C_{max} of simvastatin acid plasma concentrations.

Specific pathways of fusidic acid metabolism in the liver are not known, however, an interaction between fusidic acid and HMG-CoA reductase inhibitors, which are metabolised by CYP-3A4, can be suspected.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy (see Warnings and Precautions, *Myopathy/Rhabdomyolysis* and Interactions).

No pharmacokinetic studies have been conducted to date in elderly patients or in patients with renal or hepatic dysfunction.

Pharmaceutical Precautions

Store below 30°C. Avoid transient temperatures above 50°C.

Medicine Classification

Prescription Medicine

Package Quantities

LIPEX 10 mg, 20 mg, 40 mg and 80 mg tablets are available as blister packs of 30 tablets.

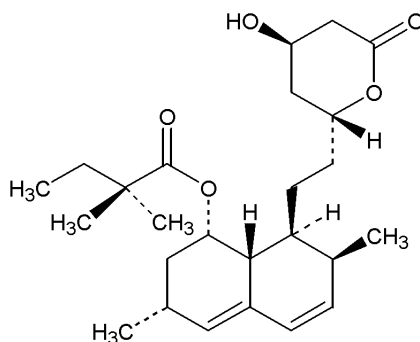
Further Information

Chemistry

LIPEX tablets contain simvastatin, which is described chemically as:

[1S[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 α β]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl-2,2-dimethylbutanoate.

Its empirical formula is C₂₅H₃₈O₅ and its molecular weight is 418.57. Its structural formula is:



Simvastatin is a white crystalline powder, practically insoluble in water and freely soluble in chloroform, methanol and ethanol.

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