

1. NAME OF THE MEDICINAL PRODUCT

Luvinsta 20 mg capsules, hard

Luvinsta 40 mg capsules, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 20 mg fluvastatin as fluvastatin sodium.

Each hard capsule contains 40 mg fluvastatin as fluvastatin sodium.

Luvinsta contains soya lecithin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

20 mg:

Capsule cap: orange, opaque marked with white imprint "20"

Capsule body: ivory, opaque marked with brown imprint "FST"

40 mg:

Capsule cap: orange, opaque marked with white imprint "40"

Capsule body: yellow, opaque marked with brown imprint "FST"

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of primary hypercholesterolaemia and mixed hyperlipidaemia (Fredrickson Types IIa and IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments is inadequate.

Luvinsta is also indicated in patients with coronary heart disease and hypercholesterolaemia for the secondary prevention of coronary events after percutaneous coronary intervention, see Section 5.1.

4.2 Posology and method of administration

Prior to initiating Luvinsta, secondary causes of hypercholesterolaemia should be excluded, and the patient placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

The capsules must be taken in the evening or at bedtime independently of meals. The capsules must be swallowed whole with a glass of water.

•*Dose recommendations for lipid lowering effect*

The recommended starting dose is 20 mg to 40 mg once daily in the evening.

A dose of 20 mg once daily may be adequate in mild cases.

Most patients will require a dose of 20 mg to 40 mg once daily but the dose may be increased to 80 mg daily (1 capsule Luvinsta 40 mg twice daily), individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

The maximum lipid-lowering effect with a given dose of the drug is achieved within 4 weeks. Doses should be adjusted according to the patient's response and dose adjustment made at intervals of 4 weeks or more. The therapeutic effect of Luvinsta is maintained with prolonged administration.

Luvinsta is efficacious in monotherapy or in combination with bile acid sequestrants. When Luvinsta is used in combination with cholestyramine or other resins, it should be administered at least 4 hours after the resin to avoid a significant interaction due to binding of the drug to the resin. Minimal data exist to support the efficacy and safety of Luvinsta in combination with nicotinic acid or fibrates (see section 4.5).

•Dose recommendations for the secondary prevention of coronary events after percutaneous coronary intervention

In patients with coronary heart disease after percutaneous coronary intervention, the dose is 80 mg daily (1 capsule Luvinsta 40 mg twice daily).

Patients with impaired kidney function

Fluvastatin is cleared by the liver, with less than 6% of the administered dose excreted into the urine. The pharmacokinetics of fluvastatin remain unchanged in patients with mild to severe renal insufficiency. No dose adjustments are therefore necessary in these patients.

Patients with impaired liver function

Luvinsta is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see section 4.3 and section 4.4).

Use in the elderly

There is no evidence of reduced tolerability or altered dosage requirements in elderly patients.

Children and adolescents with heterozygous familial hypercholesterolemia

Prior to initiating treatment with Luvinsta in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolaemia, the patient should be placed on a standard cholesterol-lowering diet. Dietary therapy should be continued during treatment.

The recommended starting dose is 40 mg (1 capsule Luvinsta 40 mg) or 80mg (1 capsule Luvinsta 40 mg twice daily). The dose of 20 mg fluvastatin (1 capsule Luvinsta 20 mg) may be adequate in mild cases. Starting doses should be individualized according to baseline LDL-C levels and the recommended goal of therapy to be accomplished.

The use of fluvastatin in combination with nicotinic acid, cholestyramine, or fibrates in children and adolescents has not been investigated.

4.3 Contraindications

Hypersensitivity to the active substance, to soya protein, peanut protein or to any of the excipients.

Patients with active liver disease, or unexplained, persistent elevations in serum transaminases.

Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

No data are available for the use of fluvastatin in patients with a rare condition known as homozygous familial hypercholesterolaemia.

The effect is expected to be low due to LDL-receptor deficiency in these patients.

Therefore use of fluvastatin is not recommended in these patients.

Liver function

As with other lipid-lowering medicinal products, it is recommended that liver function tests be performed before the initiation of treatment and at 12 weeks following initiation of treatment or elevation in dose and

periodically thereafter in all patients. Patients whose levels increase in response to the drug should be monitored particularly closely, with immediate repetition of the measurement followed by more frequent measurements. Should an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) exceed 3 times the upper limit of normal and persist, therapy should be discontinued. In very rare cases, possibly drug-related hepatitis was observed that resolved upon discontinuation of treatment.

Caution should be exercised when Luvinsta is administered to patients with a history of liver disease or heavy alcohol consumption.

Skeletal muscle

With Luvinsta, myopathy has been reported rarely, whereas myositis and rhabdomyolysis have been reported very rarely. In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of creatine kinase (CK) values, myopathy, myositis or rhabdomyolysis have to be considered. Patients should therefore be advised to report promptly unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.

Creatine kinase measurement

There is no current evidence to require routine monitoring of plasma total creatine kinase or other muscle enzyme levels in asymptomatic patients on statins. If creatine kinase has to be measured it should not be done following strenuous exercise or in the presence of any plausible alternative cause of CK-increase as this makes the value interpretation difficult.

Before the treatment

As with all other statins physicians should prescribe fluvastatin with caution in patients with pre-disposing factors for rhabdomyolysis and its complications. A creatine kinase level should be measured before starting fluvastatin treatment in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Alcohol abuse
- In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.

In such situations, the risk of treatment should be considered in relation to the possible benefit and clinical monitoring is recommended. If CK-levels are significantly elevated at baseline >5 x upper limit of normal, levels should be re-measured within 5 to 7 days later to confirm the results. If CK-levels are still significantly elevated > 5 x upper limit of normal at baseline, treatment should not be started.

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 that a patient has developed interstitial lung disease, statin therapy should be discontinued.

Whilst on treatment

If muscular symptoms like pain, weakness or cramps occur in patients receiving fluvastatin, their CK-levels should be measured. Treatment should be stopped, if these levels are found to be significantly elevated (> 5 x upper limit of normal).

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to less than ≤ 5 x upper limit of normal, treatment discontinuation should be considered.

Should the symptoms resolve and CK-levels return to normal, then re-introduction of fluvastatin or another statin may be considered at the lowest dose and under close monitoring.

The risk of myopathy is known to be increased in patients receiving immunosuppressive medicinal products (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. Minimal data exist to support the efficacy or safety of Luvinsta in combination with nicotinic acid, its derivatives, fibrates or ciclosporin. Luvinsta should be used with caution in patients receiving such concomitant medication (see section 4.5).

Hyperlipoproteinaemia

No data are available for the use of fluvastatin in patients with hyperlipoproteinaemia with a major increase in triglycerides.

Homozygous familial hypercholesterolaemia

No data are available for the use of fluvastatin in patients with a rare condition known as homozygous familial hypercholesterolaemia. The effect is expected to be low due to LDL – receptor deficiency in these patients. Therefore use of fluvastatin is not recommended in these patients.

Children and adolescents with heterozygous familial hypercholesterolemia

In patients aged <18 years, efficacy and safety have not been studied for treatment periods longer than two years. No data are available about the physical, intellectual and sexual maturation for prolonged treatment period. The long-term efficacy of Luvinsta therapy in childhood to reduce morbidity and mortality in adulthood has not been established (see section 5.1).

Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia (for details see section 5.1). In the case of pre-pubertal children, as experience is very limited in this group, the potential risks and benefits should be carefully evaluated before the initiation of treatment.

Soya lecithin

Luvinsta contains soya lecithin. Purified soya lecithin may contain soya protein. Dietary soya-products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations. The Ph. Eur. Monograph does not contain a test for residual protein.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions

Fibric acid derivatives (fibrates) and niacin (nicotinic acid)

Concomitant administration of fluvastatin with bezafibrate, gemfibrozil, ciprofibrate or niacin (nicotinic acid) has no clinically relevant effect on the bioavailability of fluvastatin or the other lipid-lowering agents. An increased risk of myopathy and/or rhabdomyolysis has been observed in patients receiving other HMG-CoA reductase inhibitors together with any of these molecules, probably because they can produce myopathy when given alone. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution (see section 4.4).

Colchicines

Myotoxicity, including muscle pain and weakness and rhabdomyolysis, have been reported in isolated cases with concomitant administration of colchicine. The benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution (see section 4.4).

Ciclosporin

Studies in renal transplant patients indicate that the bioavailability of fluvastatin (up to 40 mg/day) is not elevated to a clinically significant extent in patients on stable regimens of ciclosporin. The results from another study wherein 80 mg fluvastatin was administered to renal transplant patients who were on stable ciclosporin regimen showed that fluvastatin exposure (AUC) and maximum concentration (C_{max}) were increased by 2 fold compared to historical data in healthy subjects. Although these increases in fluvastatin

levels were not clinically significant, this combination should be used with caution. Starting and maintaining fluvastatin therapy should be in a dose as low as possible when combined with ciclosporin. Fluvastatin (40 mg and 80 mg) had no effect on ciclosporin bioavailability when co-administered.

Warfarin and other coumarin derivatives

In healthy volunteers, the use of fluvastatin and warfarin (single dose) did not adversely influence warfarin plasma levels and prothrombin times compared to warfarin alone. However, isolated incidences of bleeding episodes and/or increased prothrombin times have been reported very rarely in patients on fluvastatin receiving concomitant warfarin or other coumarin derivatives. It is recommended that prothrombin times are monitored when fluvastatin treatment is initiated, discontinued, or the dosage changed in patients receiving warfarin or other coumarin derivatives.

Rifampicin (rifampin)

Administration of fluvastatin to healthy volunteers pre-treated with rifampicin (rifampin) resulted in a reduction of the bioavailability of fluvastatin by about 50%. Although at present there is no clinical evidence that fluvastatin efficacy in lowering lipid levels is altered, for patients undertaking long-term rifampicin therapy (e.g. treatment of tuberculosis), appropriate adjustment of fluvastatin dosage may be warranted to ensure a satisfactory reduction in lipid levels.

Oral antidiabetic agents

For patients receiving oral sulfonylureas (glibenclamide [glyburide], tolbutamide) for the treatment of non-insulin-dependent (type 2) diabetes mellitus (NIDDM), addition of fluvastatin does not lead to clinically significant changes in glycemic control.

In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max} , AUC, and $t_{1/2}$ of glibenclamide approximately 50%, 69% and 121%, respectively. Glibenclamide (5 to 20 mg daily) increased the mean C_{max} and AUC of fluvastatin by 44% and 51%, respectively. In this study there were no changes in glucose, insulin and C-peptide levels. However, patients on concomitant therapy with glibenclamide (glyburide) and fluvastatin should continue to be monitored appropriately when their fluvastatin dose is increased to 80 mg per day.

Bile acid sequestrants

Fluvastatin should be administered at least 4 hours after the resin (e.g. cholestyramine) to avoid a significant interaction due to drug binding of the resin.

Fluconazole

Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the exposure and peak concentration of fluvastatin by about 84% and 44%.

Although there was no clinical evidence that the safety profile of fluvastatin was altered in patents pre-treated with fluconazole for 4 days, caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Itraconazole and erythromycin

Concomitant administration of fluvastatin with the potent cytochrome P450 (CYP) 3A4 inhibitors itraconazole and erythromycin has minimal effects on the bioavailability of fluvastatin. Given the minimal involvement of this enzyme in the metabolism of fluvastatin, it is expected that other CYP3A4 inhibitors (e.g. ketoconazole, ciclosporin) are unlikely to affect the bioavailability of fluvastatin.

Histamine H₂-receptor antagonists and proton pump inhibitors

Concomitant administration of fluvastatin with cimetidine, ranitidine, or omeprazole results in an increase in the bioavailability of fluvastatin, which, however, is of no clinical relevance.

Phenytoin

The overall magnitude of the changes in phenytoin pharmacokinetics during co-administration with fluvastatin is relatively small and not clinically significant. Thus, routine monitoring of phenytoin plasma levels is sufficient during co-administration with fluvastatin. The minimal effect of phenytoin on fluvastatin

pharmacokinetics indicates that dosage adjustment of fluvastatin is not warranted when co-administered with phenytoin.

Cardiovascular agents

No clinically significant pharmacokinetic interactions occur when fluvastatin is concomitantly administered with propranolol, digoxin, losartan, amlodipine or ACE- inhibitors. Based on the pharmacokinetic data, no monitoring or dosage adjustments are required when fluvastatin is concomitantly administered with these agents.

Food interactions

There are no apparent differences in the lipid-lowering effects of fluvastatin when administered with the evening meal or 4 hours after the evening meal. Based on the lack of interaction of fluvastatin with other CYP3A4 substrates, fluvastatin is not expected to interact with grapefruit juice.

4.6 Pregnancy and lactation

Pregnancy

Fluvastatin is contraindicated during pregnancy (see section 4.3).

For fluvastatin no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy and embryonal/foetal development (see section 5.3). Since HMG-CoA reductase inhibitors decrease the synthesis of cholesterol and possibly of other biologically active substances derived from cholesterol, they may cause foetal harm when administered to pregnant women. For these reasons, fluvastatin must not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with fluvastatin must be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

Women of childbearing potential / Contraception in males and females

Women of childbearing potential have to use effective contraception. If a patient becomes pregnant while taking fluvastatin, therapy must be discontinued.

Lactation

Fluvastatin is excreted in rat milk with a milk:plasma ratio of 2. It is not known whether fluvastatin or its metabolites are excreted in human milk. Because many medicinal products are excreted in human milk and because of the potential for serious adverse reactions, women taking fluvastatin must not breast-feed their infants (see section 4.3).

4.7 Effects on ability to drive and use machines

Luvinsta has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from available data). The most commonly reported adverse drug reactions are minor gastrointestinal symptoms, insomnia and headache.

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)

Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia
Nervous system disorders	
Common:	Headache, fatigue, dizziness.
Very rare:	Paraesthesia, dysaesthesia, hypoaesthesia and peripheral neuropathy also known to be associated with the underlying hyperlipidemic disorders.
Gastrointestinal disorders	
Common:	Dyspepsia, abdominal pain, nausea, constipation, flatulence, diarrhoea
Very rare:	Acute pancreatitis.
Skin and subcutaneous tissue disorders	
Rare:	Hypersensitivity reactions such as rash, urticaria.
Very rare:	Other skin reactions (e.g. eczema, dermatitis, bullous exanthema), face oedema, angioedema
Musculoskeletal and connective tissue disorders	
Common:	Joint pain
Rare:	Myalgia, muscle weakness, myopathy.
Very rare:	Rhabdomyolysis, myositis, lupus erythematosus-like reactions.
Vascular disorders	
Very rare: Vasculitis	
Hepatobiliary disorders	
Very rare: Hepatitis.	
Psychiatric disorders	
Common: Insomnia.	

Laboratory Findings

Confirmed elevations of transaminase levels to more than 3 times the upper limit of normal (ULN) developed in a small number of patients (less than or equal to 2%). Marked elevations of CK levels to more than 5 x ULN developed 0.3 - 1.0% of patients receiving licensed doses of fluvastatin in clinical trials.

Children and adolescents with heterozygous familial hypercholesterolemia

The safety profile of fluvastatin in children and adolescents with heterozygous familial hypercholesterolemia assessed in 114 patients aged 9-17 years treated in two open non-comparative clinical trials was similar to the one observed in adults. In both clinical trials no effect was observed on growth and sexual maturation. The ability of the trials to detect any effect of treatment in this area was however low.

4.9 Overdose

Should an accidental overdosage occur, administration of activated charcoal is recommended. In the case of a very recent oral intake gastric lavage may be considered. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors ATC code: C 10 AA 04

Fluvastatin is a racemate of the two erythro enantiomers of which one exerts the pharmacological activity.

Fluvastatin, a synthetic cholesterol-lowering agent, is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Fluvastatin exerts its main effect in the liver. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The ultimate result of these mechanisms is a reduction of the plasma cholesterol concentration.

The overall cholesterol profile is improved with the principal effects being the reduction of total-C and LDL-C. Fluvastatin also produces a moderate reduction in triglycerides and a moderate increase in HDL-C. Therapeutic response is well established within 2 weeks, and maximum response is achieved within 4 weeks from treatment initiation and maintained during chronic therapy.

In the Lescol Intervention Prevention Study (LIPS), the effect of fluvastatin on major adverse cardiac events (MACE) was assessed in patients with coronary heart disease who had first successful transcatheter therapy (TCT). The study included male and female patients (18-80 years old) and with baseline total cholesterol levels ranging from 3.5-7.0 mmol/L.

In this randomised, double-blind, placebo-controlled trial, a total of 1677 patients were recruited (844 in fluvastatin group and 833 in placebo group). The MACE was defined as cardiac death, non fatal MI and re-intervention (including CABG, repeat TCT, or TCT of a new lesion). The dose of fluvastatin used in this study was 80 mg daily over 4 years. Although the overall composite endpoint showed significant reduction in MACE (22%) compared to placebo ($p=0.013$), the individual components (cardiac death, non fatal MI and re-intervention) failed to reach statistical significance. There was however a trend in favour of fluvastatin. Therapy with fluvastatin reduced the risk of cardiac death and/or myocardial infarction by 31% ($p=0.065$).

Children and adolescents with heterozygous familial hypercholesterolemia

The safety and efficacy of fluvastatin in children and adolescent patients aged 9 - 16 years of age with heterozygous familial hypercholesterolemia has been evaluated in 2 open label, uncontrolled clinical trials of 2 years' duration. 114 patients (66 boys and 48 girls) were treated with fluvastatin administered as either fluvastatin capsules 20 mg - 40 mg bid or fluvastatin 80 mg extended release tablets using a dose-titration regimen based upon LDL-C response.

The first study enrolled 29 pre-pubertal boys, 9-12 years of age, who had an LDL-C level > 90th percentile for age and one parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dL equivalent to 5,8 mmol/L (range: 137 - 354 mg/dL equivalent to 3,6 - 9,2 mmol/L). All patients were started on fluvastatin capsules 20

mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg bid) to achieve an LDL-C goal of 96,7 to 123,7 mg/dL (2,5 mmol/L to 3,2 mmol/L).

The second study enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C > 190 mg/dL (equivalent to 4,9 mmol/L) or LDL-C > 160 mg/dL (equivalent to 4,1 mmol/L) and one or more risk factors for coronary heart disease, or LDL-C > 160 mg/dL (equivalent to 4,1 mmol/L) and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dL equivalent to 5,8 mmol/L (range: 148 - 343 mg/dL equivalent to 3,8 - 8,9 mmol/L). All patients were started on fluvastatin capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (fluvastatin 80 mg extended release tablet) to achieve an LDL-C goal of < 130 mg/dL (3,4 mmol/L).

In the first study, fluvastatin 20 to 80 mg daily doses decreased plasma levels of total-C and LDL-C by 21% and 27%, respectively. The mean achieved LDL-C was 161 mg/dL equivalent to 4,2 mmol/L (range: 74 - 336 mg/dL equivalent 1,9 - 8,7 mmol/L). In the second study, fluvastatin 20 to 80 mg daily doses decreased plasma levels of total-C and LDL-C by 22% and 28%, respectively. The mean achieved LDL-C was 159 mg/dL equivalent to 4,1 mmol/L (range: 90 - 295 mg/dL equivalent to 2,3 - 7,6 mmol/L).

The majority of patients in both studies (83% in the first study and 89% in the second study) were titrated to the maximum daily dose of 80 mg. At study endpoint, 26 to 30% of patients in both studies achieved a targeted LDL-C goal of < 130 mg/dL (3,4 mmol/L).

5.2 Pharmacokinetic properties

Absorption:

Fluvastatin is absorbed rapidly and completely (98%) following oral administration to fasted volunteers. In a fed state, the drug is absorbed at a reduced rate. Fluvastatin exerts its main effect in the liver, which is also the main organ for its metabolism. The absolute bioavailability assessed from systemic blood concentrations is 24%.

Distribution:

The apparent volume of distribution (V_z) for the drug is 330 L. More than 98% of the circulating drug is bound to plasma proteins, and this binding is unaffected by drug concentration.

The major circulating blood components are fluvastatin and the pharmacologically inactive N-desisopropyl-propionic acid metabolite. The hydroxylated metabolites have pharmacological activity but do not circulate systemically.

Biotransformation:

The hepatic metabolic pathways of fluvastatin in humans have been characterised. There are multiple, alternative cytochrome P450 (CYP450) pathways involved. However, the major pathway is mediated by CYP2C9 and this pathway is subject to potential interactions with other CYP2C9 substrates or inhibitors. In addition there are several minor pathways (e.g. CYP3A4).

Elimination:

Several detailed *in vitro* studies have addressed the inhibitory potential of fluvastatin on common CYP isoenzymes. Fluvastatin inhibited only the metabolism of compounds that are metabolised by CYP2C9. Following administration of ³H-fluvastatin to healthy volunteers, excretion of radioactivity is about 6% in the urine and 93% in the faeces, and fluvastatin accounts for less than 2% of the total radioactivity excreted. The plasma clearance (CL/f) for fluvastatin in man is calculated to be 1.8 ± 0.8 L/min. Steady-state plasma concentrations show no evidence of fluvastatin accumulation following administration of 80 mg daily. Following oral administration of 40 mg of fluvastatin, the terminal disposition half-life for fluvastatin is 2.3 ± 0.9 hours.

Children and adolescents with heterozygous familial hypercholesterolemia

No pharmacokinetic data in children are available.

5.3 Preclinical safety data

Repeat toxicity studies with fluvastatin identified a variety of changes that are common to HMG-CoA reductase inhibitors, viz. hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in

dogs, myopathy in rodents, mild liver changes in most laboratory animals, with gall bladder changes in the dog, monkey and hamster, thyroid weight increases in the rat and testicular degeneration in the hamster. Fluvastatin is devoid of the CNS vascular and degenerative changes recorded in dogs with other members of this class of compounds.

Carcinogenicity studies in rats and mice revealed a low incidence of forestomach squamous papillomas in mice and rats and one carcinoma in rats at the highest dose (18 mg/kg per day escalated to 24 mg/kg per day after 1 year). The forestomach neoplasms reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. In addition, an increase incidence of thyroid follicular cell neoplasms in male rats given the highest dose of fluvastatin was recorded. This is consistent with species-specific findings with other HMGCoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no treatment-related increases in the incidence of hepatic adenomas or carcinomas were observed.

In vitro and *in vivo* mutagenicity studies revealed no evidence of mutagenicity.

Reproductive toxicity studies indicated that fluvastatin had no adverse effects on fertility or reproductive performance in males or females, nor was it embryotoxic or teratogenic. Late gestational effects at high doses resulted in maternal mortality and fetal and neonatal lethality attributable to exaggerated pharmacological effects of fluvastatin during pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Luvinsta 20 mg:

Capsule contents:

Mannitol

Talc

Magnesium stearate

Capsule body:

Gelatin

Titanium dioxide (E171)

Iron oxide, red (E172)

Iron oxide, yellow (E172)

Capsule cap:

Gelatin

Titanium dioxide (E171)

Iron oxide, red (E172)

Printing ink:

White ink on capsule cap:

Titanium dioxide (E171)

Shellac

Soya lecithin

Antifoam DC 1510

Brown ink on capsules body:

Shellac

Iron oxide, red (E172)

Iron oxide, black (E172)

Titanium dioxide (E171)

Propylene glycol

Luvinsta 40 mg:

Capsule contents:

Mannitol

Talc

Magnesium stearate

Capsule body:

Gelatin

Titanium dioxide (E171)

Iron oxide, yellow (E172)

Capsule cap:

Gelatin

Titanium dioxide (E171)

Iron oxide, red (E172)

Printing ink:

White ink on capsule cap:

Titanium dioxide (E171)

Shellac

Soya lecithin

Antifoam DC 1510

Brown ink on capsule body:

Shellac

Iron oxide, red (E172)

Iron oxide, black (E172)

Titanium dioxide (E171)

Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Luvinsta 20 mg capsules, hard

Blister packs (OPA/Alu/PVC-Alu): 18 months

HDPE bottle: 2 years

Luvinsta 40 mg capsules, hard

Blister packs (OPA/Alu/PVC-Alu): 2 years

HDPE bottle: 2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in original container in order to protect from moisture and light.

6.5 Nature and contents of container

Blister packs (OPA/Alu/PVC-Alu).

HDPE container with desiccant (silica gel) and LDPE cap with seal.

Pack sizes:

Blister packs (OPA/Alu/PVC-Alu): 10, 14, 20, 28, 30, 50, 56, 60, 98 and 100 capsules
HDPE bottle with desiccant and LDPE cap: 28, 30, 56 and 60 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Reykjavíkurvegur 76-78,
220 Hafnarfjörður,
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

Luvinsta 20 mg: MA628/00801
Luvinsta 40 mg: MA628/00802

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20th August 2009

10. DATE OF REVISION OF THE TEXT

2nd November 2009