

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Luvinsta SR 80 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 80 mg fluvastatin (as fluvastatin sodium).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Yellow, round, biconvex tablet.

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 SR is also indicated in patients with coronary heart disease for the secondary prevention of coronary events (cardiac death, non-fatal myocardial infarction and coronary revascularisation) after percutaneous coronary intervention, see Section 5.1.

4.2 Posology and method of administration

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

• *Treatment of primary hypercholesterolaemia and mixed hyperlipidaemia (Fredrickson Types IIa and IIb)*
Luvinsta SR 80 mg prolonged release tablets are **not** suitable for treatment initiation, for this purpose alternative pharmaceutical forms and tablet strengths (20 mg and 40 mg) are appropriate.

The recommended starting dose is 20 mg to 40 mg once daily as immediate release capsule. 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 prolonged-release tablet fluvastatin 80 mg daily or 1 immediate-release capsule fluvastatin 40 mg twice daily), individualised according to the baseline LDL-cholesterol (LDL-C) levels and the recommended goal of therapy to be accomplished. The maximum recommended daily dose is 80 mg.

• *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. Luvinsta SR can be administered as a single dose at any time of the day with or without food and must be swallowed whole with a glass of water.

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 SR is maintained with prolonged administration.

When fluvastatin 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.

Children and adolescents

There is no experience with the use of fluvastatin in individuals less than 18 years of age. The product should not be used in this group of patients.

Elderly

There is no evidence of reduced tolerability or altered dosage requirements in elderly patients thus, no dose adjustment is required in such patients.

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.

Impaired liver function

Fluvastatin is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see sections 4.3 , 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see section 4.2 and 4.8).

Pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

Liver function

As with other lipid-lowering drugs, 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 fluvastatin is administered to patients with a history of liver disease or heavy alcohol consumption.

Skeletal muscle

With fluvastatin, myopathy has rarely been reported, 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 promptly report 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 >5x 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 >5x 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 (>5xULN).

If muscular symptoms are severe and cause daily discomfort, even if CK-levels are elevated to less than 5 x ULN, 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 has been reported to be increased in patients receiving immunosuppressive drugs (including ciclosporin), fibrates, nicotinic acid or erythromycin together with other HMG-CoA reductase inhibitors. However, in clinical trials in patients receiving fluvastatin in combination with nicotinic acid, fibrates, or ciclosporin, myopathy has not been observed. Isolated cases of myopathy have been reported post-marketing for concomitant administration of fluvastatin with ciclosporin and fluvastatin with colchicine. The benefits of the combined use of fluvastatin with fibrates, niacin or colchicine should be carefully weighed against the potential risks of these combinations and fluvastatin should be used with caution in patients receiving such concomitant medication (see section 4.5).

Hyperlipoproteinemia

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

Homozygous familial hypercholesterolemia

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

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 agent. 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).

Colchicine

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 patients 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

In an interaction study concomitant administration of fluvastatin and phenytoin resulted in an increase of fluvastatin mean AUC and C_{max} values by 40% and 27% respectively. This combination should be used with caution due to the increased risk of developing myopathy and/or rhabdomyolysis. Co-administration of fluvastatin (40 mg b.i.d. for 5 days) increased the mean C_{max} of phenytoin by 5% whereas the mean AUC was increased by 22%. Patients on phenytoin should be carefully monitored when fluvastatin therapy is initiated or when the dose is increased.

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

Mean AUC and C_{max} were increased by 49% and 45% respectively and t_{max} prolonged when fluvastatin was taken with food, compared to fasting state. However, no clinically obvious differences in the lipid-lowering effects and safety are anticipated when fluvastatin is taken with or without food.

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

No studies on the effects on the ability to drive and use machines have been performed.

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:

- 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: Sleep disturbances including insomnia and nightmares.	

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.

4.9 Overdose

The experience with overdoses of fluvastatin is very limited. 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% ($p=0.065$).

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_zf) 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.

Food

Mean AUC and C_{max} were increased by 49% and 45% respectively and t_{max} prolonged when fluvastatin was taken with food, compared to fasting state. However, no clinically obvious differences in the lipid-lowering effects and safety are anticipated when fluvastatin is taken with or without food.

5.3 Preclinical safety data

Acute toxicity

The estimated oral LD_{50} is > 2 g/kg in mice and > 0.7 g/kg in rats.

Repeated dose toxicity

Repeated dose 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

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 increased 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.

Mutagenicity

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

Toxicity to reproduction

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

Tablet core:

Povidone
Microcrystalline cellulose
Hydroxyethyl cellulose
Mannitol
Magnesium stearate

Film-coating:

Hypromellose 50
Macrogol 6000
Iron oxide yellow (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

Blisters: Keep the blisters in the outer carton in order to protect from light.

Glass bottle and HDPE bottle: Keep the container tightly closed in order to protect from moisture and light.

6.5 Nature and contents of container

Blister (OPA/Alu/PVC-Alu). Pack sizes of 10, 20, 28, 30, 50, 60, 98 and 100 prolonged release tablets.

HDPE bottle with desiccant and snap-on cap (LDPE) with a tamper evident ring. Desiccants are HDPE plastic canisters filled with activated silica gel. Pack sizes of 250 prolonged release tablets.

Round, brown glass container closed with rubbed plastic cap (HDPE) with thread including seal. Desiccants are HDPE plastic canisters filled with activated silica gel.

Pack sizes of 250 prolonged release tablets

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)

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