NOVARTIS

Drug Safety & Epidemiology/Integrated Medical Safety

Fluvastatin

XUO320

EU Safety Risk Management Plan Elements for a Public Summary

Active substance(s) (INN or common name):	Fluvastatin
Pharmacotherapeutic group (ATC Code):	HMG-CoA reductase inhibitors (C10A A04)
Name of Marketing Authorization Holder / Applicant:	Novartis Europharm Limited
Number of medicinal products to which this RMP refers:	1
Product(s) concerned (brand name(s)):	Lescol / Lescol XL
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1 Part VI.2 Elements for a Public Summary

1.1 Part VI.2.1 Overview of disease epidemiology

High cholesterol is an increased level of cholesterol in the blood. Alone, high cholesterol usually has no symptoms, but it can have serious health effects. High cholesterol can cause narrowed arteries (called atherosclerosis). Therefore, high cholesterol increases the risks of vascular diseases like heart disease and stroke. Cholesterol levels usually increase steadily with age, more steeply in women, and stabilize after middle age. Worldwide, high cholesterol levels are found in 39% of the adult population over 25 years of age.

Coronary Heart Disease (CHD), the most common type of cardiovascular disease, is caused by fatty deposits from cholesterol building up along the inner walls of the arteries of the heart. This narrows the arteries and reduces blood flow to the heart. CHD may affect individuals at any age but is more common in older people, nearly tripling with each decade of life. Males are affected more than females.

1.2 Part VI.2.2 Summary of treatment benefits

Treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia:

In 12 studies in patients with high cholesterol, Lescol was administered to 1,621 patients in daily doses of 20 mg, 40 mg and 80 mg (40 mg twice daily) for 6 weeks or more versus placebo tablets (does not contain any drug). Results after 24-weeks of treatment showed lowering of total cholesterol from 17% to 27% on all daily doses of 20 mg, 40 mg and 80 mg of Lescol.

Lescol XL was administered as a single daily dose of 80 mg to over 800 patients in 3 pivotal trials that lasted 24 weeks each and the results showed that total cholesterol was reduced by 19% compared to baseline.

In a randomized, double-blind trial of fluvastatin compared to placebo in patients with coronary heart disease who had a first successful percutaneous coronary intervention (a non-surgical procedure used to treat the narrowed arteries of the heart), 884 patients received fluvastatin 80 mg and 833 patients received placebo daily for 4 years. The patients treated with fluvastatin had 22% lower risk of the first major adverse cardiac event (cardiac death, non-fatal myocardial infarction or coronary revascularization) compared to patients who received placebo.

1.3 Part VI.2.3 Unknowns relating to treatment benefits

In the main and supporting studies most patients were Caucasian but in later studies many ethnic groups and children were also evaluated. There is no evidence that the effectiveness of Lescol is different in any age or ethnic groups. Patients with certain genetic disorders that affect fat metabolism may have reduced or no response to Lescol or other medications similar to Lescol (called Statins).

1.4 Part VI.2.4 Summary of safety concerns

Table 1-1 Important identified risks

Risk	What is known	Preventability
Liver failure /Death *(Severe hepatic disorder)*	Lescol/Lescol XL should not be used in patients with active liver disease, or unexplained, persistent raised liver function blood tests (liver enzymes).There have been some cases of fatal and non-fatal liver failures with some statins including Lescol/Lescol XL, although a causal relationship with Lescol/Lescol XL treatment has not been determined.	Yes, by monitoring liver function, limiting alcohol ingestion, and using caution when administering Lescol/Lescol XL to patients with a history of liver disease or heavy alcohol ingestion.
Allergic reactions *(Hypersensitivity (rash, urticaria)/* angioedema/*anaphylaxis))*	There have been some cases of allergic reactions with patients taking Lescol/Lescol XL. It should not be used in patients with known allergy to fluvastatin or any of its components.	Preventability is unknown at this time but patients should be monitored for symptoms of allergic reactions.
Severe muscle deterioration *(Rhabdomyolysis*)	Reports of patients experiencing rhabdomyolysis while taking Lescol/Lescol XL are very rare. Rhabdomyolysis is investigated in patients with unexplained muscle tenderness or weakness or an unexplained rise in the enzyme called creatine kinase (CK).	Yes, by monitoring patients for unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.
Developing diabetes *(New onset diabetes mellitus)*	Some evidence suggests that the class of drugs similar to Lescol (called Statins) cause a rise in blood sugar, which may require diabetes treatment in some cases. It is considered that the risk of high blood sugar is outweighed by the benefits of the statins, making it not necessary to stop the drug for this reason.	Yes, by monitoring patients at risk for diabetes.
A disease affecting tissue and space around the air sacs in the lung *(Interstitial lung disease)*	Rare cases of interstitial lung disease have been reported with some products similar to Lescol (called statins), especially with long term therapy.	Yes, by monitoring patients for symptoms of this disease.
Muscle deterioration caused by an immune reaction (*Immune-mediated necrotizing myopathy*)	Muscle deterioration associated with statin use (Lescol / Lescol XL) is a new and emerging entity that supports a link between statin use and IMNM and raises the questions of distinct clinical phenotypes and treatment strategy.	Yes, by monitoring patients for unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Risk	What is known	Preventability
Drug interaction with drugs which work like fluconazole (*Interaction with strong CYP 2C9 inhibitor (fluconazole))*	In healthy volunteers, the use of Lescol/Lescol XL and fluconazole, resulted in an increase in the amount of Lescol/ Lescol XL in the blood.	Yes, by exercising caution when patients are taking Lescol / Lescol XL as well as fluconazole.
Drug interaction with drugs which work like rifamipin (*Interaction with strong CYP 2C9 inducer (rifampicin))*	In healthy volunteers, the use of Lescol/Lescol XL and rifampicin (rifampin) resulted in reduced level of Lescol / Lescol XL by about 50% .	Yes, by adjusting the dosage of Lescol / Lescol XL so that it will still work to lower the cholesterol level in the blood.
Drug interaction with blood thinners (*Interaction with coumarin derivatives (warfarin))*	In healthy volunteers, the use of Lescol/Lescol XL and blood thinners like warfarin (single dose) did not affect the level of blood thinners or the patient blood clotting times.	Yes, by monitoring clotting times of the blood when the patient is also on blood thinning drugs at the same time as Lescol / Lescol XL.
Drug interaction with anti-diabetic drug (glibenclamide)	In diabetic patients on glibenclamide and taking Lescol / Lescol XL, the amount to glibenclamide in the blood increased by 50% or more but this did not affect the patient's blood sugars.	Yes, by monitoring patients with diabetes who are treated with glibenclamide at the same time as Lescol / Lescol XL 80 mg.

Table 1-2 Important potential risks

Risk	What is known
Use during pregnancy	There is insufficient data on the use of fluvastatin during pregnancy. Since statins decrease the amount of cholesterol made by the body and possibly of other substances which are made from cholesterol, they may cause foetal harm when administered to pregnant women. Therefore, Lescol/Lescol XL should not be used during pregnancy.
A disease of the tendon *(Tendinopathy)*	The exact cause of tendinopathies is not fully understood and different stresses may cause varying responses. There are many theories for tendinopathy and if pain is experienced early treatment is recommended to prevent serious injury.
Drug interaction with colchicine (Pharmacodynamic interaction with colchicine)	Toxic damage to the muscles, including muscle pain and weakness and severe muscle damage, has been reported in isolated cases when Lescol / Lescol XL was taken at the same the patient was taking colchicines.
Drug interaction with some the following drugs: Bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin (*Pharmacodynamic interaction with other drugs*)	An increase in the chances of moderate to severe muscle damage has been seen in patients receiving this type of cholesterol lowering drug together with any of these drugs.

Table 1-3 Missing information

Risk	What is known
Use in children under 9 years of age	Fluvastatin has only been investigated in children of 9 years and older with inherited high cholesterol condition. Therefore there is no data available for children under 9 yrs old.
Use during breast feeding	Based on research, fluvastatin may pass into breast milk. But there is not enough information on how this effects the infant.

1.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

1.6 Part VI.2.6 Planned post authorization development plan

1.6.1 Studies which are a condition of the marketing authorization

Not applicable.

1.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.