NOVARTIS

Drug Safety & Epidemiology

Fluvastatin

XUO320

EU Safety Risk Management Plan

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
Document status:	Final
Version number	1.2
Data lock point for this RMP	31-Aug-2013
Date of final sign off	26-Nov-2014

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List of abbreviations

AE	Adverse event
ALF	Acute liver failure
ALT	Alanine transaminase
AMI	Acute myocardial infarction
ARIC	Atherosclerosis Risk in Communities Study
AST	Aspartate transaminase / aspartate aminotransferase
ATS/ERS	American thoracic society/European respiratory society
AUC	Area under curve
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CHD	Coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK	Creatine kinase
CNS	Central nervous system
DDD	Defined daily dose
DM	Diabetes mellitus
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies
GPRD	General Practice Research Database
HA	Health Authority
HbA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
HLT	High level term
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HMGCR	3-hydroxy-3-methyl-glutaryl-CoA reductase
HMO	Health maintenance organization
IBM	Inclusion body myositis
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
INR	International normalized ratio
IPF	Idiopathic pulmonary fibrosis
IR	Incidence rate
LDL	Low-density lipoprotein
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction

MRP	Mutual recognition procedure
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NHS	National Health services
NIDDM	Non-insulin dependant diabetes mellitus
NPI	National prescribing information
PCI	Percutaneous coronary intervention
PhV	Pharmacovigilance
PhVWP	Pharmacovigilance Working Party
PIL	Patient information leaflet
PSUR	Periodic Safety Update Report
PTY	Patient treatment years
PY	Person/Patient years
QPPV	Qualified person for Pharmacovigilance
RMP	Risk Management Plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA query
SOC	System organ class
STEMI	ST-elevation (Q-wave) myocardial infarction
T2DM	Type 2 Diabetes mellitus
TGA	Therapeutic goods administration
ULN	Upper limit normal
VLDL	Very low density lipoprotein
WHO	World Health Organization

Changes from previous RMP version

This is the version 1.2 of the Lescol Risk Management Plan (RMP). RMP version 1.1 was amended to meet a commitment mentioned in the Final variation assessment report (FVAR) from the Federal Institute for Drugs and Medical Devices (BfArM), Germany. This version (version 1.2) includes updates to the risk minimization activities for potential risk Tendinopathy following its inclusion in the SmPC.

Based on the preliminary variation assessment report (PVAR) of the RMS (Germany – BfArM) on RMP version 1.0, the following key changes were introduced in RMP version 1.1 compared to the previous RMP request:

- Non-clinical data added.
- Identified and potential risk of drug-drug interaction added.
- Identified risk of "immune-mediated necrotizing myopathy" added.
- Terminology for potential risk of 'Foetal harm' is now changed to 'Use during Pregnancy'
- Missing information added: 'Use in paediatric patients < 9 years of age' and 'Use during lactation'.

The list below shows the major modifications/changes for Safety Risk Management Plan (RMP) Version 1.0.

RMP Document Section	Description of changes
Part I	Administrative changes (sign-off date updated)
Part II Module SI	None
Part II Module SII	Non-clinical data added.
Part II Module SIII	Reference to Article 10a of European directive corrected to GVP Module V, Section C.3.1
Part II Module SIV	Reference to Article 10a of European directive corrected to GVP Module V, Section C.3.1
Part II Module SV	None.
Part II Module SVI	None.
Part II Module SVII	Pharmacological class effects of 'Immune-mediated necrotizing myopathy', an important identified risk, and 'Tendinopathy', an important potential risk, are added for fluvastatin. Potential risk of 'Foetal harm' is rephrased as 'Use during Pregnancy.'
Part II Module SVIII	Important identified risks: • 'Immune-mediated necrotizing myopathy' is added as important identified risk for fluvastatin. • Drug-drug interaction with strong CYP 2C9 inhibitor (fluconazole) and inducers (rifampicin), coumarin derivatives (warfarin) and with anti-diabetic drugs (glibenclamide) are added as important identified risk for fluvastatin. Important potential risks: • Potential risk of 'Foetal harm' is rephrased as 'Use during Pregnancy.' • Pharmacodynamics drug-drug interaction with colchicine and other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid),

RMP Document Section	**Description of changes**
	erythromycin, cyclosporin) are added as important potential risks.
	Missing information:
	Use in paediatric patients < 9 years of age and use during lactation added.
Part III	Pharmacovigilance plan for newly added risks and missing information have been added.
	Potential risk of 'Foetal harm' is rephrased as 'Use during Pregnancy.'
Part IV	None.
Part V	Risk minimization measures for newly added risks and missing information have been added.
	Potential risk of 'Foetal harm' is rephrased as 'Use during Pregnancy.'
	Objective of the risk minimization measures for Use during pregnancy has been updated.
Part VI	Updated to reflect newly added risks (identified, potential, and pharmacological class effects) and missing information.
	Element for public summary has been updated.

Part VII Annexes	
Annex number	Description of changes
Annex 1	None
Annex 2	SmPC was revised and attached.
Annex 3	None.
Annex 4	None.
Annex 5	None.
Annex 6	None.
Annex 7	None.
Annex 8	None.
Annex 9	None.
Annex 10	None.
Annex 11	None.
Annex 12	New literature reference added.

1 Part I: Product Overview

1.1 Administrative information on the RMP

Table 1-1 Administrative information on the RMP

Part	Module/Annex	Date last updated for submission (sign off date)	Version number of RMP when last submitted or Not Applicable
Part II	SI	07-Oct-2014	1.1
Safety Specification	Epidemiology of the indication and target population(s)		
	SII	07-Oct-2014	1.1
	Non-clinical part of the safety specification		
	SIII	07-Oct-2014	1.1
	Clinical trial exposure		
	SIV	07-Oct-2014	1.1
	Populations not studied in clinical trials		
	SV	07-Oct-2014	1.1
	Post-authorization experience		
	SVI	07-Oct-2014	1.1
	Additional EU requirements for the safety specification		
	SVII	07-Oct-2014	1.1
	Identified and potential risks		
	SVIII	07-Oct-2014	1.1
	Summary of the safety concerns		
Part III		07-Oct-2014	1.1
Pharmacovigilance Plan			
Part IV		07-Oct-2014	1.1
Plan for post-authorization			
efficacy studies			
Part V		07-Oct-2014	1.1
Risk Minimization Measures			
Part VI		07-Oct-2014	1.1
Summary of RMP			
Part VII	Annex 2	07-Oct-2014	1.1
Annexes	Current or proposed SmPC/PIL		
	Annex 3	07-Oct-2014	1.1
	Worldwide marketing status by		

Part	Module/Annex	Date last updated for submission (sign off date)	Version number of RMP when last submitted or Not Applicable
	country		
	Annex 4 Synopsis of clinical trial program	07-Oct-2014	1.1
	Annex 5 Synopsis of pharmacoepidemiological study program	07-Oct-2014	1.1
	Annex 6 Protocols for proposed and on-going studies in Part III	07-Oct-2014	1.1
	Annex 7 Specific adverse event follow-up forms	07-Oct-2014	1.1
	Annex 8 Protocols for studies in Part IV	07-Oct-2014	1.1
	Annex 9 Synopsis of newly available study reports in Parts III-IV	07-Oct-2014	1.1
	Annex 10 Details of proposed additional risk minimization activities	07-Oct-2014	1.1
	Annex 11 Mock up examples	07-Oct-2014	1.1
	Annex 12 Other supporting data	07-Oct-2014	1.1

QPPV name: Philippe Close

QPPV signature: [QPPV Signature page]

Contact person for this RMP: [redacted]

E-mail address or telephone number of contact person: [redacted]

Overview of versions:

Not

1.2 For each product in the RMP

Invented names in the European Economic Area (EEA):	Lescol/ Lescol XL (Locol, Cranoc, Lipaxan, Primesin, Canef, Liposit, Vaditon, Digaril, Lescol Depot, Fluvastatin Novartis, Lescol MR, Lescol Exel, Lescol LP, Lescol Prolib, Liposit Prolib, Vaditon Prolib, Digaril Prolib).
Authorization procedure:	Mutual Recognition Procedure (MRP)
Brief description of the product including: chemical class: summary of mode of action: important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines:	Fluvastatin sodium (Lescol/Lescol XL) is a water-soluble, fully synthetic mevalonolactone derivative available as a racemic mixture, consisting of both active and inactive enantiomers. Fluvastatin, a cholesterol-lowering agent, is a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the enzyme responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. Fluvastatin exerts its main effect in the liver as the inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, stimulating the synthesis of low density lipoprotein (LDL) receptors, and thereby increasing the uptake LDL particles. The ultimate result is a reduction in the plasma cholesterol concentration. Lescol and Lescol XL reduce total-C, LDL-C, Apo B, and triglycerides, and increase of high density lipoprotein (HDL) C in patients with hypercholesterolaemia and mixed dyslipidaemia.
Indications in the EEA:	<u>Dyslipidaemia:</u> Treatment of adults with primary hypercholesterolaemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. <u>Secondary prevention in coronary heart disease:</u> Secondary prevention of major adverse cardiac events in adults with coronary heart disease after percutaneous coronary interventions (see SmPC section 5.1). Proposed (if applicable): Not Applicable.
Posology and route of administration in the EEA:	Adults <u>Dyslipidaemia</u> Prior to initiating treatment with Lescol/Lescol XL, patients should be placed on a standard cholesterol-lowering diet, which should be continued during treatment. Starting and maintenance doses should be individualized according to the baseline LDL-C levels and the treatment goal to be accomplished. The recommended dosing range is 20 to 80 mg/day. For patients requiring LDL-C reduction to a goal of < 25% a starting dose of 20 mg may be used as one capsule in the evening. For patients requiring LDL-C reduction to a goal of ≥25%, the recommended starting dose is 40 mg as one capsule in the evening. The dose may be uptitrated to 80 mg daily, administered as a single dose (one Lescol XL tablet) at any time of the day or as one 40 mg capsule given twice daily (one in the morning and one in the evening). The maximum lipid-lowering effect with a given dose is achieved

within 4 weeks. Dose adjustments should be made at intervals of 4 weeks or more.

Secondary prevention in coronary heart disease

In patients with coronary heart disease after percutaneous coronary interventions the appropriate daily dose is 80 mg.

Lescol is efficacious in monotherapy. When Lescol is used in combination with cholestyramine or other resins, it should be administered at least 4 hours after the resin to avoid significant interaction due to binding of the drug to the resin. In cases where coadministration with a fibrate or niacin is necessary, the benefit and the risk of concurrent treatment should be carefully considered (for use with fibrates or niacin see SmPC Section 4.5).

Paediatric population

Children and adolescents with heterozygous familial hypercholesterolaemia

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

The recommended starting dose is one 20 mg Lescol capsule. Dose adjustments should be made at 6-week intervals. Doses should be individualised according to baseline LDL-C levels and the recommended goal of therapy to be accomplished. The maximum daily dose administered is 80 mg either as Lescol capsules 40 mg twice daily or as one Lescol 80 mg tablet once daily.

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

Lescol/Lescol XL has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia.

Renal Impairment

Lescol/Lescol XL 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 however, due to limited experience with doses >40mg/day in case of severe renal impairment (Creatinine Clearance <0.5 mL/sec or 30 mL/min), these doses should be initiated with caution.

Hepatic Impairment

Lescol/Lescol XL is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see SmPC Sections 4.3, 4.4 and 5.2).

Elderly population

No dose adjustments are necessary in this population.

Method of administration

	Lescol capsules and Lescol XL tablets can be taken with or without meals and should be swallowed as whole with a glass of water.	
	Proposed (if applicable): Not Applicable.	
Pharmaceutical forms and strengths:	Capsules, hard; 20 mg & 40 mg Prolonged-release tablets; 80 mg Proposed (if applicable): Not Applicable.	
Country and date of first authorization worldwide:	United Kingdom	23-Aug-1993
Country and date of first launch worldwide:	United Kingdom	31-Jan-1994
Country and date of first authorization in the EEA:	United Kingdom	23-Aug-1993
Is the product subject to additional monitoring in the EU?	No	

2 Part II Safety Specification Module SI: Epidemiology of the indications and target population

2.1 Indication

Brand names of concerned products (with this indication)

Lescol/Lescol XL indicated for dyslipidaemia and secondary prevention in coronary heart disease in Europe.

2.1.1 Part II Module SI.1. Epidemiology of the disease

Incidence and prevalence

Dyslipidemia

The two main lipids found in blood are cholesterol and triglycerides. There are few incidence numbers published for hypercholesterolemia because it is a chronic condition with an unclear onset, making it difficult to quantify new cases.

In 2008, the global prevalence of raised total cholesterol among adults aged ≥25 years was 39% (WHO 2010). The prevalence of elevated total cholesterol was highest in the WHO European Region (54% for both sexes), followed by the WHO Region of the Americas (48% for both sexes). The WHO African Region and the WHO South-East Asia Region showed the lowest percentages (23% and 30% respectively). The prevalence of raised total cholesterol increased noticeably according to the income level of the country. In low-income countries, around a quarter of adults had raised total cholesterol, in lower-middle income countries this rose to around a third of the population for both sexes. In high-income countries, over 50% of adults had raised total cholesterol (WHO 2010).

Coronary heart disease (CHD)

The WHO MONICA (monitoring trends and determinants in cardiovascular disease) Project estimated the incidence of CHD in 37 different populations in 21 countries (including 29 populations in 16 European countries). The incidence of coronary events (a definite or likely myocardial infarction [MI]-heart attack) was higher in Northern, Central and Eastern Europe than in Southern and Western Europe (with the exception of the UK). The CHD event rate in adults aged 35-64 years ranged from 210 (Spain-Catalonia) to 835 (Findland-North Karelia) events per 100,000 population (Tunstall-Pedoe et al 1999).

The annual incidence of hospital admission for any acute MI varied between 90–312/100 000 inhabitants/year and the incidence of hospital admissions for STEMI alone between 44–142/100000 inhabitants/year across Europe in 2005-2008 (Widimsky et al 2010).

Demographics of the target population – age, sex, race/ethnic origin

Dyslipidemia

Prevalence of raised cholesterol can vary widely among adults from different countries. In 2008, according to the WHO Global Health Observatory national estimates of the prevalence of raised blood cholesterol levels (both the proportion of the population in excess of 5.0 mmol/L and in excess of 6.2 mmol/L), the highest prevalence of raised cholesterol levels was seen in the high income countries of Northern and Western Europe, while the lowest prevalence was seen in countries of the former Soviet Union. The population with the lowest proportion of adults aged 25 years and older with raised blood cholesterol levels was Tajikistan, where 24% of the population had levels above 5.0 mmol/L and less than 5% had levels above 6.2 mmol/L. In contrast, Iceland had 70% of the population with blood cholesterol levels above 5.0 mmol/L and 29% with levels above 6.2 mmol/L. In high income countries with high proportions of the population with raised cholesterol levels, the proportion of men with raised cholesterol generally exceeded that of women. In countries with low rates of raised cholesterol, more women than men were affected (Nichols et al 2012).

In the US population, an estimated 31.9 million adults ≥20 years of age have total serum cholesterol levels ≥240 mg/dL (extrapolated to 2010 by use of The National Centre for Health Statistics (NCHS)/National Health and Nutrition Examination Survey (NHANES) 2007–2010 data), with a prevalence of 13.8% (Table 2-1) (Go et al 2013).

Table 2-1 Prevalence High Total and LDL Cholesterol and Low HDL Cholesterol, US population, 2010

Population group	Total Cholesterol ≥200 mg/dL	Total Cholesterol ≥240 mg/dL	LDL Cholesterol ≥130 mg/dL	HDL Cholesterol <40 mg/dL
Both sexes	43.4%	13.8%	31.1%	21.8%
Males	41.3%	12.7%	31.9%	31.8%
Females	44.9%	14.7%	30.0%	12.3%

Source of data: National Health and Nutrition Examination Survey (2007–2010), National Center for Health Statistics, and National Heart, Lung, and Blood Institute. Estimates from National Health and Nutrition Examination Survey 2007–2010 (National Center for Health Statistics) applied to 2010 population estimates (Go et al 2013).

The prevalence of abnormal lipid levels among youths 12 to 19 years of age is 20.3%; 14.2% of normal-weight youths, 22.3% of overweight youths, and 42.9% of obese youths have at least 1 abnormal lipid level (NHANES 1999–2006, NCHS) (CDC 2010).

Approximately 7.8% of adolescents 12 to 19 years of age have total cholesterol levels ≥200 mg/dL (NHANES 2007–2010, unpublished NHLBI tabulation). There are limited data available on LDL cholesterol for children 4 to 11 years of age. High levels of LDL cholesterol occurred in 7.3% of male adolescents and 7.6% of female adolescents during 2007 to 2010 (CDC 2010).

The age-adjusted prevalence of high LDL cholesterol in US adults was 25.3% in 1999 to 2004 (NHANES/NCHS). Low levels of HDL cholesterol occurred in 21.7% of male adolescents and 10.7% of female adolescents during 2007 to 2010 (NHANES 2007–2010, unpublished NHLBI tabulation) (Go et al 2013).

There are limited data available on triglycerides for children 4 to 11 years of age. High levels of triglycerides occurred in 9.4% of male adolescents and 6.7% of female adolescents during 2007 to 2010 (CDC 2010). A fasting triglyceride level ≥150 mg/dL in adults is considered elevated. Approximately 27% of adults ≥20 years of age had a triglyceride level ≥150 mg/dL during 2007 to 2010 (NHANES 2007–2010, unpublished NHLBI tabulation) (Ford et al 2009, Go et al 2013).

Coronary heart disease

An estimated 15.4 million Americans ≥20 years of age has CHD. Based on data from the NHANES 2007-2010 the total CHD prevalence is 6.4% in US adults ≥20 years (7.9% for men and 5.1% for women) and MI is 4.2% for men and 1.7% for women. The estimated annual incidence of MI is 525,000 new attacks and 190,000 recurrent attacks. In the Atherosclerosis Risk in Communities Surveillance study, in participants 35 to 74 years of age, the average age-adjusted first MI or fatal CHD rates per 1000 population were as follows: white men, 3.9; black men, 5.5; white women, 1.7; and black women, 3.4 (unpublished data from ARIC Surveillance 1987–2009, NHLBI) (Go et al 2013).

Risk factors for the disease

Dyslipidemia

Dyslipidemia is one of the major risk factors for cardiovascular disease and coronary heart disease. Cholesterol increases the risks of heart disease, stroke and other vascular diseases. Globally, one third of ischaemic heart disease is attributable to high blood cholesterol (WHO 2009).

Coronary heart disease

Risk factors for CHD including hypercholesterolemia, hypertension, diabetes, obesity and smoking act synergistically to increase CHD risk (Wilson et al 1998). In terms of attributable deaths, the leading cardiovascular risk factor globally is raised blood pressure (to which 13% of global deaths is attributed), followed by tobacco use (9%), raised blood glucose (6%), physical inactivity (6%) and overweight and obesity (5%) (WHO 2009).

Main treatment options

Dyslipidemia

Management of cholesterol problems may include both lifestyle and diet changes as well as drug therapy.

Commonly prescribed classes of treatment, according to the National Cholesterol Education Program, include:

- HMG-CoA reductase inhibitors (statins: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin). These agents work by inhibiting the rate-limiting enzyme in the formation of cholesterol, and cause a reduction in the level of circulating LDL cholesterol.

- Bile acid-binding resins (cholestyramine, colesevelam, and colestipol), which bind bile acids in the intestine, which causes a drop in enterohepatic bile circulation. In response, the liver increases production of bile acids, which uses up hepatic cholesterol. This causes a drop in plasma LDL levels.
- Niacin, which causes reduction in LDL.
- Fibric acid derivatives (gemfibrozil, fenofibrate, clofibrate, and bezafibrate). They act by reducing the synthesis and increasing the breakdown of very low density lipoprotein (VLDL) particles, with secondary effects on LDL and HDL levels.

Ezetimibe is a lipid-lowering drug that inhibits the intestinal absorption of dietary and biliary cholesterol by blocking passage across the intestinal wall. It reduces LDL.

Coronary heart disease

The goal in treating MI is the restoration of normal blood flow and salvage of the remaining myocardium. The primary treatments utilized for acute MI patients include antiplatelet therapy and reperfusion therapy (thrombolytic therapy and percutaneous interventions).

The current recommendation is to treat patients with STEMI who seek medical attention within 12 hours of the onset of symptoms with reperfusion therapy, either primary percutaneous coronary intervention (PCI) or thrombolytic therapy. Patients without ST-segment elevation (previously labeled "non-Q wave" infarctions) do not benefit, and may derive harm, from thrombolysis.

After the first 24 hours, the focus of patient management is to prevent recurrent ischemia, improve infarct healing and prevent remodeling, and prevent recurrent vascular events. Patients with haemodynamic compromise, who are at high risk for death, need careful monitoring and management of volume status.

Postinfarction management should begin with identification and modification of risk factors. Treatment of hyperlipidemia and smoking cessation both prevent recurrent infarction and death. LDL cholesterol levels should be lowered below 100 mg/dL, and probably to a goal of 70 mg/dL, with a statin started prior to discharge. Blood pressure control and cardiac rehabilitation or exercise are also recommended.

Mortality and morbidity (natural history)

Dyslipidaemia

As with blood pressure, the risks of cholesterol are continuous and extend across almost all levels seen in different populations. Observational research indicates a linear relationship, with a 20% increase in risk of CHD for each 10% increase in serum cholesterol. This dose-response effect occurs at any level of cholesterol and is apparent in both men and women and blacks and whites (Wilson et al 1998, Stamler et al 1986).

Coronary heart disease

In 2012 was the most common cause of death in the world (Finegold et al 2012). CHD by itself is the single most common cause of death in Europe: accounting for 1.8 million deaths in Europe each year. Over one in five women (22%) and one in five men (20%) die from the

disease. CHD is also the single most common cause of death in the EU, accounting for over 681,000 deaths in the EU each year: 15% of deaths among men, and 13% of deaths among women (Nichols et al 2012).

The discharge rates for CHD in Europe have remained at slightly over 800 per 100,000 population since 2006. In the EU, hospital discharge rates for CHD were over 600 per 100,000 population. Evidence from several European countries has demonstrated that a substantial proportion of the observed reductions in coronary heart disease mortality in recent decades has been due to reductions in case fatality rates. There remain large differences, however, even between high income European countries. Reported admission-based case fatality rates in 21 European OECD countries show more than three-fold differences in acute myocardial infarction (AMI) case fatality rates, from 2.3% in Denmark to 8.6% in Belgium (Nichols et al 2012).

2.1.2 Part II Module SI.2. Concomitant medications in the target population

Dyslipidaemia

Hypercholesterolaemic patients on statins are likely to be on multiple drugs. Because the metabolic link of hypercholesterolemia to other disorders (hypertension, glucose intolerance, hyperuricaemia), statins can frequently be prescribed together with drugs used to treat this disorders. Besides, as risk factor of CHD and stroke, it can be frequently prescribed together with drugs used in secondary prevention of CHD.

Coronary heart disease

Post-infarction management involves identification and modification of risk factors. Treatment of hyperlipidemia with lipid lowering medications, blood pressure control with different classes of anti-hypertension medications (i.e. beta blockers, nitrates, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers), and long-term antithrombotic therapy are common.

2.1.3 Part II Module SI.3. Important co-morbidities found in the target population

Dyslipidemia

Hypercholesterolemia seldom occurs in isolation from other cardiovascular risk factors. It tends to occur in association with other atherogenic risk factors that promote its occurrence and greatly influence its cardiovascular disease impact. Hypercholesterolemia appears to be metabolically linked to hypertension, glucose intolerance, abdominal obesity, hyperinsulinemia, and hyperuricemia, among others.

During the period from 1999 to 2006, 26.0% of US adults had hypercholesterolemia, 9% of adults had both hypercholesterolemia and hypertension, 1.5% of adults had DM and hypercholesterolemia, and 3% of adults had all 3 conditions (Fryar et al 2010).

Coronary heart disease

Data from the INTERHEART study, a large standardized case-control study of incident acute MI in 52 countries, have shown that prevalence of diabetes, hypertension, obesity and abnormal lipid concentrations is higher among MI patients than controls (Yusuf et al 2004). The prevalence of metabolic syndrome (i.e. the clustering of metabolic abnormalities including abdominal obesity, elevated glucose, abnormal lipids, and elevated blood pressure) was 22.1% (95%CI: 21.1% to 23.1%), using the WHO definition, and 28.1% (95% CI: 27.0% to 29.2%), using the IDF definition, among MI cases (Mente et al 2010).

3 Part II Safety Specification Module SII: Non-clinical part of the safety specification

Fluvastatin sodium is a cholesterol lowering agent that competitively inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in converting HMG-CoA to mevalonate to produce cholesterol. This results in the inhibition of cholesterol synthesis, which then stimulates low-density lipoproteins (LDL) receptors to increase LDL particle uptake. (Micromedex 2014). Fluvastatin sodium belongs to the lipophilic statins.

The toxicity information for fluvastatin sodium has been obtained from preclinical company study reports and company expert summaries. All preclinical toxicity studies were fully GLP compliant, whereas pharmacodynamics and pharmacokinetic studies were conducted prior to the adoption of GLPs.

Table 3-1 Key Safety findings (from non-clinical studies)

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including:	
Single and repeat-dose toxicity,	In a placebo-controlled study including 40 hypercholesterolemic patients, doses up to 320 mg/day (n=7 per dose group) administered as Lescol XL 80 mg tablets over two weeks were well tolerated (CDS 2011).
Acute oral single dose studies were conducted in mice, rats, rabbits and hamsters. Fluvastatin has low acute oral toxicity in all species tested (LD_{50} > 500 mg/kg). A splayed gait was noted at a minimum dose of 300 mg/kg (rabbit), 500 mg/kg (rats) and 2500 mg/kg (mice). Histopathologic examination of rats displaying this gait revealed oedema in the ventral spinal tracts of the thoracico/lumbar regions and the sciatic nerve. No inflammation or loss of myelin was seen. In repeat dose studies this sign only occurred in rats dosed with 50 mg/kg BID, which was a lethal dose in less than 4 weeks (Prentice 1992).	
The safety of fluvastatin was extensively investigated in repeat dose toxicity studies in rats, rabbits, dogs, monkeys, mice and hamsters. A variety of changes were identified that are common to HMG-CoA reductase inhibitors, for example hyperplasia and hyperkeratosis of the rodent non-glandular stomach, cataracts in dogs, myopathy in rodents, mild liver changes in most laboratory animals, with gallbladder changes in 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 (Prentice 1992).	Only limited reports on drug induced liver injury (DiLi) associated with statins are available (Björnsson et al 2012). Hepatotoxicity may also include effects of statins on glucose metabolism. A lipophilic statin (simvastatin) can inhibit glucose induced cytosolic calcium *in vitro* (Parmar and Mehta 2009).
Reproductive In a study in rats at dose levels in females of 0.6, 2 and 6 mg/kg per day and in males of 2, 10 and 20 mg/kg per day, fluvastatin had no adverse	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. Therefore,

Key Safety findings (from non-clinical studies)	Relevance to human usage
effects on the fertility or reproductive performance. **Developmental toxicity** In spite of clear evidence of maternal toxicity, particularly in rabbits, fluvastatin is devoid of embryotoxic and teratogenic potential. A pre- and post-natal development study at dose levels of 2, 6, 12 and 24 mg/kg per day during late gestation and early lactation in rats showed maternal mortality at or near term and post-partum accompanied by foetal and neonatal lethality at 6 mg/kg per day and above caused by cardiotoxicity. In a third study, pregnant rats were administered 12 or 24 mg/kg per day during late gestation until weaning of the pups, with or without the presence of concurrent supplementation with mevalonic acid, a derivative of HMG-CoA that is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the cardiotoxicity and the maternal and neonatal mortality. Therefore, the maternal and neonatal lethality observed with fluvastatin reflects its exaggerated pharmacologic effect during pregnancy. **Genotoxicity** In a standard battery of *in vitro* and *in vivo* studies, no genotoxic potential for fluvastatin was demonstrated. **Carcinogenicity** The fore stomach neoplasms observed in rats and mice reflect chronic hyperplasia caused by direct contact exposure to fluvastatin rather than a genotoxic effect of the drug. The increased incidence of thyroid follicular cell neoplasms in male rats given fluvastatin appears to be consistent with species-specific findings with other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no treatment-related increases in the incidence of hepatic adenomas or carcinomas were observed (Prentice 1992).	Lescol/Lescol XL is contraindicated during pregnancy Delays in skeletal development were noted at doses of approximately twice the human exposure (based on human equivalent dose comparison). However, no adverse reproductive outcomes were seen at doses up to 6 mg/kg/day in rats (Zarek et al 2013).
General safety pharmacology cardiovascular (including potential for QT interval prolongation) nervous system etc.	None.
Mechanisms for drug interactions	None.
Other toxicity-related information or data	None.

Summary of Nonclinical Data

In nonclinical studies, fluvastatin caused several toxicities that are typical of drugs that inhibit HMG-CoA reductase: inflammation and squamous papilloma in rats, lenticular cataracts in dogs, gall bladder inflammation and mucosal hyperplasia, and myopathy. Histologic CNS changes occurred in mice, rats and dogs at high doses. No observed effect level (NOEL) doses for these changes were determined in long term studies. Fluvastatin is devoid of the CNS vascular changes recorded in dogs with other members of this class of compounds.

3.1 Part II Module SII.1. Conclusions on non-clinical data

Table 3-2 Safety concerns from non-clinical data

Safety concerns
Important identified risks (confirmed by clinical data)
None
Important potential risks (not refuted by clinical data or which are of unknown significance)
Delays in skeletal development, teratogenicity. Diabetes, and hepatic toxicity may all be due to pleiotropic pharmacological effects.
Missing information
None

4 Part II Safety Specification Module SIII Clinical trial exposure

The active substance “fluvastatin” of the medicinal product has well-established medicinal use within the community for more than ten years, with recognised efficacy and an acceptable level of safety. Therefore, under GVP Module V, Section V.C.3.1, module SIII is not required.

5 Part II Safety Specification Module SIV: Populations not studied in clinical trials

The active substance “fluvastatin” of the medicinal product has well-established medicinal use within the community for more than ten years, with recognised efficacy and an acceptable level of safety. Therefore, under GVP Module V, Section V.C.3.1, module SIV is not required.

6 Part II Safety Specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Action taken by regulatory authorities and/or marketing authorization holders for safety reasons.

During the period covered by this RMP (01-Sep-2009 to 31-Aug-2013), there has been no marketing authorization withdrawal or suspension, no failure to obtain a marketing authorization (MA) renewal, no restrictions on distribution, and no clinical trial suspension for safety reasons. Furthermore, there were no dosage modifications, formulation changes, changes in target population, or changes in indications for safety reasons.

The table below summarizes, for the period from 01-Sep-2009 to 31-Aug-2013, regulatory actions taken worldwide with regards to risk / issue as presented in PSUR 17 (01-Sep-2009 to 31-Aug-2012) and Addendum Report (01-Sep-2012 to 31-Aug-2013).

Table 6-1 Cumulative list

Country(ies)	Action taken	Date
Class labeling changes in Europe and the United States of America (USA)		
European Union (EU), Iceland, and Norway	An Article 30 referral, which aims at harmonizing the national Summary of Product Characteristics (SmPC) in all EU Members States as well as Iceland and Norway, was initiated on 19-Feb-2009. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) provided its opinion to the European Commission (EC) on a harmonized SmPC on 19-Nov-2009 and the EC issued its decision on 15-Mar-2010. The main areas of disharmony in the national SmPCs that were addressed during the referral included: Section 4.1 (Therapeutic indications), Section 4.2 (Posology and method of administration), Section 4.3 (Contraindications) and Section 4.4 (Special warnings and precautions for use). The harmonized SmPC, proposed in the referral for Lescol and Lescol XL and its clones also incorporated the Pharmacovigilance Working Party's (PhVWP) recommendations for a class label in Oct-2009. An update to the section 'Special warnings and precautions for use' to include interstitial lung disease and the addition of the following adverse events reported with some statins under the section 'Undesirable effects': sleep disturbances, including insomnia and nightmares, memory loss, sexual dysfunction, depression, exceptional cases of interstitial lung disease, especially with long term therapy. Following the publication of a meta-analysis in 2010 that reported that therapy with class of HMG-CoA reductase inhibitors (statins) was associated with a slightly increased risk for the development of new onset diabetes (NOD), the PhVWP conducted a review of this risk based on all the available data, both published and unpublished, and concluded that statins may increase the risk of new onset diabetes in patients already at risk of developing the disease. In a report dated Dec-2011, the PhVWP indicated that patients at risk need monitoring; however, the risk-benefit balance remains clearly positive. The marketing authorization holders (MAHs) were subsequently requested to include a warning in the product information of all statins authorized in the EU aiming to monitor patients at risk. Updates of SmPC sections 4.4 (Special warnings and precautions) and 4.8 (Undesirable effects) to implement the class label were made for Lescol/Lescol XL and its duplicates via Mutual Recognition Procedure (MRP) type IB variations approved on 04-Jun-2012 and 20-Jun-2012.	Oct-2009 Jun-2012
United States of America	The Food and Drug Administration (FDA) approved the Physician Labeling Rule (PLR) format for the Lescol and Lescol XL label on 17-Jun-2011 and included the following as a class label change under section 6.3 Post marketing Experience: *There has been rare post-marketing reports of cognitive* impairment *(e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have*	17-Jun-2011 28-Feb-2012

Country(ies)	Action taken	Date
	been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks). On 28-Feb-2012, FDA issued a Drug Safety Communication on its website for safety label changes to cholesterol-lowering statin drugs regarding removal of routine monitoring of liver enzymes, potential for generally non-serious and reversible cognitive side effects (memory loss, confusion, etc.) and reports of increased blood sugar and glycosylated haemoglobin (HbA1c) levels.	
Class labeling changes in other countries: Following the health authorities (HAs') respective assessments of statins in Europe and the USA, the following actions were taken:		
Canada	Based on Health Canada's request for a class labeling update in 2010, the following changes were made to section 'Adverse drug reaction' of the Canadian Product Monograph (PM): Mood related disorders including depression. A statement was added regarding reports of rare cases of interstitial lung disease with statins especially with long term therapy.	2010
Korea	Based on PhVWP report dated Nov-2009 in European Union, Korean HA requested the addition of a warning regarding exceptional cases of interstitial lung disease, especially with long-term therapy and following adverse drug reactions to the section 'Adverse reactions' of National Prescribing information (NPI): Neuropsychiatric system: Memory loss, depression Respiratory system: Exceptional cases of interstitial lung disease, especially with long-term therapy.	07-Dec-2009
Australia	In 2011, the Therapeutic Goods Administration (TGA) requested the following changes in sections 'Special warnings & precautions' and 'Undesirable effects', which were adopted on 01-Dec-2011: A statement was added regarding reports of exceptional cases of interstitial lung disease with some statins, especially with long term therapy. Inclusion of text recommending the interruption of use of statins in patients needing systemic treatment with fusidic acid. On 02-Mar-2012, TGA posted an alert on its website based on FDA Drug Safety Communication dated 28-Feb-2012 for safety label changes to cholesterol-lowering statin drugs regarding removal of routine monitoring of liver enzymes, potential for generally non-serious and reversible cognitive side effects (memory loss, confusion, etc.) and reports of increased blood sugar and glycosylated haemoglobin (HbA1c) levels.	01-Dec-2011
Jordan	On 21-Mar-2012, Health Authority JFDA requested the addition of information regarding non-serious reversible cognitive side effects (memory loss, confusion etc.) to section 'Adverse drug reactions' of NPI. A dear doctor letter (DDL) was issued on 10-Apr-2012 for safety related labeling changes regarding removal of routine monitoring of liver enzymes, non-serious reversible cognitive side effects (memory loss, confusion etc.) and increase in blood sugar levels with statin use.	21-Mar-2012

6.2 Part II Module SV.2. Non-study post-authorization exposure

6.2.1 Part II Module SV.2.1. Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in kilogram of active substance sold during the PSUR 17 review period and the defined daily dose (DDD).

6.2.2 Part II Module SV.2.2. Exposure

The sales volume of Lescol during the PSUR 17 review period (01-Sep-2009 to 31-Aug-2012) was approximately 84757.6 kg (active ingredient) for Novartis Pharma and 9991.2 kg for Sandoz. The DDD for Lescol/Lescol XL is 40 mg. The estimated exposure for the current review period was approximately 6.5 million patient treatment years (PTY). In comparison, the estimated patient exposure was approximately 35.9 million PTY for cumulative period.

The sales volume of Lescol during the review period of Lescol PSUR 17 addendum report (01-Sep-2012 to 31-Aug-2013) was approximately 19721.92 kg (active ingredient) for Novartis Pharma and 2383.68 kg for Sandoz. The DDD for Lescol is 40 mg. The estimated exposure for the current review period was approximately 1.51 (Pharma: 1.35 and Sandoz: 0.16) million patient treatment years.

6.3 Part II Module SV.3. Post-authorization use in populations not studied in clinical trials

There is no post-authorization data available on fluvastatin from its use in population which were not studied during the clinical development.

6.4 Part II Module SV.4. Post-authorization off-label use

An analysis of the indications presented in the adverse event reports received during the review period of 01-Sep-2009 to 31-Aug-2013 revealed following unapproved indications (with number of reports): Hepatitis C (n=9), hepatic steatosis (n=1), chronic hepatitis (n=1), muscle spasms (n=1), arrhythmia (n=1), hypertension (n=3), nephrotic syndrome (n=1) and musculoskeletal discomfort (n=1).

Overall, upon reviewing all the off label reports at aggregate level it is concluded that there are no new emerging safety concerns. Most of the off label reports (except Spontaneous reports) are investigated in more detail and literature articles supported that these reports are from protocol initiated controlled studies.

Age Group Analysis

An analysis of the age groups presented in adverse event reports did not reveal any specific issue with regard to specific age groups, including use in the paediatric population.

Table 6-2 Distribution of age in adverse reaction reports

Age group (range in years)	Number of reports
Neonate (0-1)	1
Infant (1-2)	2
Child (3-12)	1

Age group (range in years)	Number of reports
Adolescent (13-17)	0
Adult (18-69)	661
Elderly (70+)	365
Not reported	467
Total	**1497**

An analysis of the age groups presented in adverse event reports did not reveal any specific issue with regard to specific age groups, including use in the paediatric population (see table above).

6.5 Part II Module SV.5. Epidemiological study exposure

No epidemiological studies have been conducted for fluvastatin.

7 Part II Safety Specification Module SVI: Additional EU requirements for the safety specification

7.1 Part II Module SVI.1. Potential for harm from overdose

Lescol overdose has been studied in a placebo controlled study and doses up to 320mg/day of Lescol XL 80mg tablets over 2 weeks are well tolerated. There is no specific treatment available for Lescol/Lescol XL overdose. Should an overdose occur, the patient should be treated symptomatically and supporting measures should be taken. Special emphasis should be given to doing liver function tests and measuring serum creatine kinase (CK) levels.

7.2 Part II Module SVI.2. Potential for transmission of infectious agents

The manufacturer of Lescol declares that Lescol is a medicinal product for which no starting materials are used as defined in section 2 of the "Note for guidance on Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMEA/410/01 rev 3, effective as of 1-Jul 2011). Lescol contains an excipient of animal origin within the gelatin capsule. In addition, Lescol/Lescol XL capsules and tablets are administered by the oral route. The potential for transmission of infectious agents is, therefore, unlikely.

7.3 Part II Module SVI.3. Potential for misuse for illegal purposes

From post-marketing experience, a few cases of intentional misuse or abuse have been reported with Lescol/Lescol XL all dosage and indications. The applicant considers the potential for misuse for illegal purposes as unlikely.

7.4 Part II Module SVI.4. Potential for medication errors

The potential for medication error with Lescol is low. The naming of the product is sufficiently different from existing medications therefore the likelihood of error in dispensing is low. The packaging is unique and clearly labeled. The instructions for use are clear and simple.

7.4.1 Part II Module SVI.4.1. Description of medication errors during the clinical trial program

No medication/dispensing errors were identified during clinical development.

7.4.2 Part II Module SVI.4.2. Preventive measures for the final product being marketed

Prevention of error due to wrong medication

Routine risk minimization measures are considered sufficient.

Prevention of error due to wrong dose (strength, form, concentration)

Routine risk minimization measures are considered sufficient.

Prevention of error due to wrong route of administration

Routine risk minimization measures are considered sufficient.

7.4.3 Part II Module SVI.4.3. Effect of device failure

Not applicable.

7.4.4 Part II Module SVI.4.4. Reports of medication errors with the marketed products

Cumulatively (with DLP of 31-Aug-2012 for PSUR 17), there have been 90 reports describing 94 medication errors distributed as shown in the table below:

Table 7-1 Cumulative overview of medication errors

Medication error	Number of HCP reports	Number of non-HCP reports
Incorrect drug dosage form administered	0	1
Incorrect dose administered	0	3
Accidental exposure	18	5
Drug dose omission	1	3
Wrong technique in drug usage process	2	4
Drug dispensing error	6	2
Drug administration error	3	7
Accidental overdose	13	1
Expired drug administered	3	0
Medication error	10	8
Drug prescribing error	0	1
Inappropriate schedule of drug administration	1	0
Wrong drug administered	1	0
Underdose	1	0
Total	**59**	**35**

Based on the reports described above from PSUR 17, there were no new risks identified especially pertaining to safety and no specific actions considered necessary. The potential for medication errors is considered to be limited, and is followed in routine pharmacovigilance.

7.5 Part II Module SVI.5. Potential for off-label use

An analysis of the indications presented in the adverse event reports received during the review period of Lescol PSUR 17 revealed following unapproved indications (with number of reports): Hepatitis C (n=9), hepatic steatosis (n=1), chronic hepatitis (n=1), muscle spasms (n=1), arrhythmia (n=1), hypertension (n=3), nephrotic syndrome (n=1) and musculoskeletal discomfort (n=1).

Overall, upon reviewing all the off label reports at aggregate level it is concluded that there are no new emerging safety concerns. Most of the off label reports (except spontaneous reports) are investigated in more detail and literature articles supported that these reports are from protocol initiated controlled studies.

7.6 Part II Module SVI.6. Specific paediatric issues

As per PSUR 17 and its addendum report there are no specific paediatric issues.

7.6.1 Part II Module SVI.6.1. Issues identified in paediatric investigation plans

No paediatric investigation plan has been implemented.

7.6.2 Part II Module SVI.6.2. Potential for paediatric off-label use

Dyslipidaemia in Paediatric population is not an approved indication in the EU. Lescol/Lescol XL has been studied as an adjunct to diet for the reduction of elevated total-C, LDL-C, apo B and TG levels and for the increase of HDL-C in children and adolescents aged 9 years and older with heterozygous familial hypercholesterolemia. Therefore, the potential for off-label use exists in this population.

7.7 Part II Module SVI.7. Conclusions

There is no safety concern from this module.

8 Part II Safety Specification Module SVII: Identified and potential risks (Non-ATMP version)

8.1 Part II Module SVII.1. Newly identified safety concerns (since this module was last submitted)

Not applicable as this is the first RMP for fluvastatin.

8.2 Part II Module SVII.2. Recent study reports with implications for safety concerns

Not applicable as this is the first RMP for fluvastatin.

8.3 Part II Module SVII.3. Details of important identified and potential risks from clinical development and post-authorization experience (including newly identified)

Table 8-1 Important identified risk: Severe hepatic disorder

Risk	Severe hepatic disorder
Frequency with 95% CI	The frequency of Hepatobilliary disorders (SOC): Hepatitis is listed as very rare (<1/10,000) per EU SmPC.
Seriousness/outcomes	Post marketing cases of fatal and non-fatal hepatic failures have been reported with some statins including Lescol/Lescol XL. Although a causal relationship with Lescol/Lescol XL treatment has not been determined.
Severity and nature of risk	A causal association between severe hepatic disorder and Lescol has not been established based on the analysis of reports from Novartis safety database and publications in literatures. Severe liver events are described in the SmPC, including warnings and precautions to help minimize risks of severe hepatic events. Overall the frequency and severity trend of hepatic disorders since last 12 years as provides evidence for decreasing hepatic AEs, perhaps due, in part, to warnings and precautions within the SmPC. **1+, Mild**: Raised serum aminotransferase or alkaline phosphatase levels or both, but total serum bilirubin <2.5 mg/dL and no coagulopathy (INR <1.5). **2+, Moderate**: Raised serum aminotransferase or alkaline phosphatase levels or both and total serum bilirubin level ≥2.5 mg/dL or coagulopathy (INR >1.5) without hyperbilirubinemia. **3+, Moderate to Severe**: Raised serum aminotransferase or alkaline phosphatase levels and total serum bilirubin level >2.5 mg/dL and hospitalization (or preexisting hospitalization is prolonged) because of the drug induced liver injury. **4+, Severe**: Raised serum aminotransferase or alkaline phosphatase levels and serum bilirubin >2.5 mg/dL and at least one of the following: Prolonged jaundice and symptoms beyond 3 months, or Signs of hepatic decompensation (INR >1.5, ascites, encephalopathy), or Other organ failure believed to be related to drug induced liver injury. **5+, Fatal**: Death or liver transplantation for drug induced liver injury.
Background incidence/prevalence	Acute liver failure (ALF) is rare. Reports from the developed world suggest an overall incidence of between one and six cases per million people every

Risk	Severe hepatic disorder
	year (as per review by Bernal et al 2010). Population-based surveillance for acute liver failure in the USA (2000-2004) reported an estimated 1,600 cases of ALF per year, which yielded an annualized incidence for all causes of ALF of 5.5 (95% CI 4.3-7.0) cases per million (Bower et al 2007). There are limited studies in the literature assessing incidence or prevalence of liver enzyme elevation in the general population. However, Weil et al (2008) reviewed data collected in clinical trials conducted between 1985 and 2005 and reported a prevalence of abnormal ALT level ranging from 0.005% and 0.076%. In the USA, (National Health and Nutrition Examination Survey [NHANES] 1999–2002), the estimated prevalence of elevated ALT, AST, or either ALT or AST were 8.9%, 4.9%, and 9.8%, respectively, in the entire population and 7.3%, 3.6%, and 8.1%, respectively, after excluding participants who tested positive for hepatitis C virus antibody or reported excessive alcohol consumption (Ioannou et al 2006). Tragni et al (2007) retrospectively evaluated the baseline liver enzyme levels in a cohort of 14,120 patients before initiation of statin therapy in Italy. Hepatic disease was present in 2.9% of patients. Among patients with AST and ASL measured before treatment (33% and 32% of total cohort, respectively) the prevalence of values higher that 1x or 3x upper normal limits (UNL) were the following: 1.3% AST ≥1xULN, 0.1% AST ≥3xULN, 3.7% ALT ≥1xULN, and 0.1% ALT ≥3xULN. A medical record linkage database cohort study based on Dutch data found an incidence rate of hepatic impairment of 0.6 (95% confidence interval [CI] 0.2-1.2) per 10,000 person-years in a general population without statin exposure (Goettsch et al 2006).
Risk groups or risk factors	Race: Black, Latino, Asian, Men ages 30-40, Women ages 35-60, Alcohol ingestion, Liver disease, Genetic factors, comorbidities: infection, cancer, autoimmune disorders.
Potential mechanisms	Not known.
Preventability	Patients should be advised to report any potential symptoms or signs of hepatic failure (e.g. nausea, vomiting, loss of appetite, jaundice, impaired brain function, easy bruising or bleeding), and treatment discontinuation should be considered (SmPC). As with other lipid-lowering agents, 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. Should an increase in aspartate aminotransferase or alanine aminotransferase 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 (SmPC). Caution should be exercised when Lescol/Lescol XL is administered to patients with a history of liver disease or heavy alcohol ingestion (SmPC).
Impact on individual patient	Hepatic failure is an important risk especially in patients with pre-existing liver disease or previous history of risk factors such as hepatitis, liver metastases. These patients will have to be monitored closely.
Potential public health impact of safety concern	Can be considered life threatening. Impact on quality of life in severe cases and if complications occur.

Risk	Severe hepatic disorder
Evidence source	Well-documented individual case safety report (ICSRs), clinical trials, epidemiology data and literatures as cited above.
MedDRA terms	Hepatitis, non-infectious" SMQ (broad), Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ).

Table 8-2 Important identified risk: Hypersensitivity (rash, urticaria)/ angioedema/anaphylaxis

Risk	Hypersensitivity (rash, urticaria)/angioedema/anaphylaxis for >severity, frequency, and specificity.
Frequency with 95% CI	The frequency of Immune system disorders (SOC): Hypersensitivity reactions (rash, urticaria) is listed as rare (≥1/10,000, <1/1,000); Anaphylactic reaction is listed as very rare (<1/10,000) as per EU SmPC.
Seriousness/outcomes	Post marketing cases of Hypersensitivity have been reported with some statins including Lescol/Lescol XL.
Severity and nature of risk	A causal association between Hypersensitivity, Angioedema and Anaphylaxis and Lescol has not been established based on the analysis of reports from Novartis safety database and publications in literatures. Hypersesitivity, Angioedema and Anayphylaxis events are described in the SmPC. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment). Treatment with fluvastatin is contraindicated in patients with hypersensitivity to the active substance, to other derivatives, or to any of the excipients.
Background incidence/prevalence	The incidence of anaphylaxis in the unexposed population varies and is often underreported, partially because of the absence of a standard definition. Only a few epidemiological studies have been published, however the incidence rate estimates seem to be increasing in the last years. In the UK, a study provided incidence rate estimates for the UK general population during a 10-year period (1996-2005). The estimated annual incidence rate of anaphylaxis (per 100,000 person-years) by gender and age groups are reported in the following table:

Age Gender	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Male	12.5	32.0	15.0	36.8	18.7	8.7	23.2
Female	18.0	31.7	27.1	18.1	14.2	23.5	31.6

Overall, the estimated gender-and-age adjusted incidence rate for the general population was 21.8 per 100,000 patient-years (95% CI: 18.1-26.0) (Gonzalez-Perez et al 2010).

A previous population-based assessment carried out using the UK (General Practice Research Database (GPRD) database for the period 1994-1999 estimated a lower overall incidence rate of 8.4/100,000 patient-years (Peng and Jick 2004).

Sheikh et al (2008) also analyzed one of the largest national healthcare databases (QRESEARCH) and estimated for the UK population in 2005 an age-and-sex standardized incidence rate of 7.9/100,000 patient-years (95% CI: 7.0-9.0), assessing an increasing trend with respect to 2001 (IR: 6.7;

Risk	Hypersensitivity (rash, urticaria)/angioedema/anaphylaxis for >severity, frequency, and specificity.
	95% CI: 5.7-7.7). Sheikh and Alves (2001) studied the age, sex, geographical and socio-economic variations in hospital admission for anaphylaxis in England between 1991 and 1994, using the National Health Service (NHS) database. The estimated incidence rate for the general population aged ≥55 years was 8.2/100,000 patient-years (95% CI: 7.5-9.0), half the incidence observed among children. No relevant differences were observed between men and women, while the highest admission rates corresponded to the predominantly rural environments. The International Collaborative Study of Severe Anaphylaxis 1998, estimated the incidence of hospital-acquired anaphylaxis in Budapest (Hungary), Barcelona (Spain) and Bombay (India) areas. The observed rates of definite/probable anaphylaxis were very similar: 14.9/100,000 admissions in Budapest, 15/100,000 in Barcelona and 20/100,000 in India. Overall, among patients aged 60 years or more, the incidence rate was lower, about 12/100,000 patients and in general rates were higher in women (21/100,000) than in men (15/100,000). An Italian study (Pastorello et al 2001) reported the estimated incidence of general anaphylactic reactions (anaphylaxis symptoms in referred patients) and confirmed severe anaphylaxis in the emergency room department of a general hospital in Milan during 1997 and 1998. Overall, the observed rate of admission for anaphylaxis was unusually high: 0.36%. The incidence rates of severe anaphylaxis and general anaphylactic reactions (presence of symptoms) were 33.6/100,000 and 328/100,000, respectively. The risk of anaphylactic shock in the general population was estimated in a Danish study (Sorensen et al 1989) in a hospital area during a 13-year period. The estimated incidence rate was 3.2/100,000 inhabitants per year. More recently, (Peng and Jick 2004) estimated that an anaphylactic shock with hypotension requiring urgent treatment was present in about 10% of anaphylaxis cases. The corresponding incidence rate estimate was about 0.84/100,000 patient-years. A study based on a retrospective population-based cohort (Minnesota, 1983-1987) reported an overall incidence rate of 21 per 100,000 person-years (Yocum et al 1999). However, a subsequent study (Decker et al 2006) on another resident population in Minnesota for the period 1990-2000 estimated a higher overall gender-and-age adjusted incidence rate of 49.3 per 100,000 (95%CI: 44.6-54.1). An analysis of an hospital discharge dataset from the Florida Agency for Health Care Administration for the calendar year 2001 (Mulla and Simon 2007) estimated an overall annual hospital discharge rate for anaphylaxis of 2.8/100,000 population. In men and women aged more than 60 years, the discharge rate was about 4 to 7 per 100,000. A study by (Poulos et al 2007) analyzed the trends in hospitalization for anaphylaxis between two periods (1993-1994 and 2004-2005). The 2004-2005 estimated hospitalization rate for patients aged 65 years and over was about 8/100,000 population for anaphylaxis not caused by food, and about 1.8/100,000 for anaphylaxis caused by food. Overall, the annual rate of hospital admissions for anaphylaxis in the period 2004-2005 was about 9-10 cases per 100,000. Sheikh et al (2008) estimated the trend in lifetime prevalence of anaphylaxis in England by analyzing the QRESEARCH health care database. In 2001 the

Risk	Hypersensitivity (rash, urticaria)/angioedema/anaphylaxis for >severity, frequency, and specificity.
	overall prevalence rate was 50/100,000 patients (95% CI: 47.5-52.7), and it increased up to 75.5/100,000 (95% CI: 72.4-78.7) in 2005. The prevalence rates by older age categories in 2005 were approximately the following:

Age Gender	60-64	65-69	70-74	75-79	80+
Male	80	90	90	80	30
Female	100	110	110	60	50

	(prevalence rates are estimated approx. from a reported graph) Neugut et al (2001) estimated that 1.2% to 16.8% of the total US population can be considered at risk of an anaphylactic reaction and 0.002% may die. The estimated prevalence rates of anaphylactic reactions were the following: 4/10,000 due to food, 0.7% to 10% for penicillin, 0.22% to 1% for radio-contrast media and 0.5% to 5% after insect stings.
Risk groups or risk factors	There is a contraindication in patients with known hypersensitivity to fluvastatin or any of the excipients.
Potential mechanisms	Unknown.
Preventability	Monitoring patients for symptoms of allergic reactions.
Impact on individual patient	Can be considered life threatening. Impact on quality of life in severe cases and if complications occur.
Potential public health impact of safety concern	High.
Evidence source	As cited above.
MedDRA terms	Hypersensitivity (SMQ).

Table 8-3 Important identified risk: Rhabdomyolysis

Risk	Rhabdomyolysis for >severity, frequency, and specificity
Frequency with 95% CI	The frequency of Musculoskeletal and connective tissue disorders (SOC): Myalgia, muscular weakness, myopathy are listed as rare rare (≥1/10,000, <1/1,000); Rhabdomyolysis, lupus like syndrome, myositis); very rare (<1/10,000) as per EU SmPC.
Seriousness/outcomes	Myopathy has rarely been reported with fluvastatin. Myositis and rhabdomyolysis have been reported very rarely.
Severity and nature of risk	In patients with unexplained diffuse myalgias, muscle tenderness or muscle weakness, and/or marked elevation of CK values, myopathy, myositis or rhabdomyolysis have to be considered.
Background incidence/prevalence	Published data on the epidemiology of rhabdomyolysis are scarce. The exact incidence of rhabdomyolysis is difficult to establish, because different definitions have been used. In the US about 26,000 cases of rhabdomyolysis are reported annually in the national hospital patient discharge database (Graves and Gillum 1997 cited in Sauret et al 2002). In a retrospective analysis using the United Kingdom-based General Practice Research Database, 25 patients out of 2.5 million in a base population of patients aged 20-75 years were found to have rhabdomyolysis between 1990 and 1999 (Black and Jick 2002). However, because until recently rhabdomyolysis was not incorporated as a specific code in the common disease coding systems, some possible cases of rhabdomyolysis may not have been identified (Black

Risk	Rhabdomyolysis for >severity, frequency, and specificity
	and Jick 2002). A medical record linkage database cohort study based on Dutch data found a rhabdomyolysis incidence rate of 0.09 (95% CI 0.0-0.5) per 10,000 person-years in a general population without statin exposure (Goettsch et al 2006) while a cohort study based on Health Maintenance Organization (HMO) data from the US found a rhabdomyolysis incidence rate of 2 (95% CI 1-4) per 10,000 person-years in patients without diabetes and without statin exposure. The proportion of patients in this cohort identified with rhabdomyolysis during follow-up was 0.07% (95% CI 0.03-0.10%) (Nichols and Koro 2007).
Risk groups or risk factors	Alcohol abuse, muscle overexertion, muscle compression use of certain medications or illicit drugs, toxic substances and genetic factors
Potential mechanisms	Rhabdomyolysis (a severe form of myopathy) is the rapid breakdown (lysis) of skeletal muscle tissue (rhabdomyo) due to: • Traumatic or muscle compression (e.g., crush syndrome or prolonged immobilization) • Nontraumatic exertional (e.g., marked exertion in untrained individuals, hyperthermia, or metabolic myopathies) • Nontraumatic nonexertional (e.g., drugs or toxins, infections, or electrolyte disorders)
Preventability	Patients should therefore be advised to promptly report unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever. There is no current evidence to require routine monitoring of plasma total CK or other muscle enzyme levels in asymptomatic patients on statins. If CK 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.
Impact on individual patient	Impact on quality of life in severe cases and if complications occur.
Potential public health impact of safety concern	Unknown.
Evidence source	As cited above.
MedDRA terms	Rhabdomyolysis (SMQ).

Table 8-4 Important identified risk: New onset diabetes mellitus

Risk	New onset diabetes mellitus for >severity, frequency, and specificity
Frequency with 95% CI	Data not available.
Seriousness/outcomes	Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate.
Severity and nature of risk	This risk is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment.
Background incidence/prevalence	Several epidemiological studies assessed the incidence of T2DM in Europe as well as the US. T2DM incidence rates range between 1.1 to 16.9/1000 person-years (PY) depending on age, sex, country or ethnicity. The T2DM incidence increases with age and is slightly higher in men than in women.

Risk	New onset diabetes mellitus for >severity, frequency, and specificity Incidence rates peak around 60-69 years in men and 70-79 years in women. In a prospective, population-based study a northeastern Italian population aged 40-79 years, (Bonora et al 2004) found the following T2DM incidence rates (IRs) per 1000 PY (95% CI): Men: 8.3 (5.4-11.2), women: 8.1 (5.3-10.9). IRs increased with age, i.e., from 3.4 (1.1-5.7) when aged 40-49 years to 9.5 (4.4-14.6) in the 70-79 years old stratum, with the highest IR of 11.9 (7.2-16.6) seen in the 60-69 years group. In the German branch of MONICA (Monitoring Trends and Determinants on Cardiovascular Diseases) cohort study in individuals aged 35-74 years, the age-standardized T2DM IRs per 1000 PY were 5.8 and 4.0 in men and women, respectively. The corresponding numbers in the 35-44 years age stratum were 2.9 and 1.1 and increased to 7.5 and 6.6 in the 65-74 years age group (Meisinger et al 2002). In a 10-year prospective study in 584 Spanish patients ≥ 30 years of age, the age-adjusted cumulative T2DM annual IR was 8 per 1000 persons (Vazquez et al 2000). In a population-based study using data from the UK General Practice Research Database (GPRD), the IR of diabetes in a sample of adults ≥ 30 years of age from the general population ranged between 2.6 to 6.2 per 1000 PY (Brauchli et al 2008). In a Norwegian population-based prospective cohort study, 26,168 diabetes-free men and women aged 25-98 years were followed up from 1994 through 2005. The age-standardized IR identified was 2.6 (95% CI 2.3-2.9) and 1.6 (95% CI 1.4-1.8) per 1000 PYs in men and women, respectively. Both age- and gender-specific incidence rates increased by age and peaked in age group 60-69 years in men and 70-79 years in women (Joseph et al 2010). From 1997 to 2003, the annual incidence of diagnosed diabetes in U.S. adults aged 18-79 years of age increased from 4.9 to 6.9 per 1,000 population (Geiss et al 2006). In 2013, a total of 592 million people are estimated to have diabetes worldwide, a number that may go up to 592 million in 2035. The diabetes prevalence in the population aged 20-79 years in the European Region is estimated 8.5% and in the North American region (11%) (International Diabetes Federation 2013). Incidence rates of diabetes in patients of similar characteristics as patients initiating statins therapy but who are non-exposed to statins have been reported in recent cohort studies. In a UK general practice database the estimated incidence of T2DM in unexposed adult patients 50-84 years was 11.3 per 1,000 PYs (Danaei et al 2013). In a population-based retrospective cohort study in Taiwanese adult patients (mean age 63 years) the cumulative incidence of T2DM among non-users of statins was 20.8% after 10 years of follow-up (Wang et al 2012).
Risk groups or risk factors	Genetics, disease of pancreas, infection, illness, obesity.
Potential mechanisms	Unknown.
Preventability	Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.
Impact on individual patient	Impact on quality of life in severe cases and if complications occur.

Risk	New onset diabetes mellitus for >severity, frequency, and specificity
Potential public health impact of safety concern	Unknown.
Evidence source	As cited above.
MedDRA terms	Hyperglycaemia/new onset diabetes mellitus (SMQ broad).

Table 8-5 Important identified risk: Interstitial lung disease

Risk	Interstitial lung disease >severity, frequency, and specificity
Frequency with 95% CI	Data not available.
Seriousness/outcomes	Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy.
Severity and nature of risk	Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever).
Background incidence/prevalence	Interstitial lung disease (ILD) comprises a very large group of more than 200 different entities, several of which are relatively rare and of unknown etiology. For many of the ILDs there is still a paucity of epidemiologic data in the published literature (Karakatsani et al 2009). Crude incidence density of all ILD, as reported from population-based studies and in which cases were identified through multiple sources (i.e. not only through pulmonologists), was between 26.1 and 32.5 per 100,000 person-years (PY), whereas incidence rates were lower in studies using only pulmonologists for case identification (between 3.62 and 7.6 per 100,000 PY). Coultas et al (1994) established a population-based registry of subjects with ILD aged at least 18 years in Bernalillo County in New Mexico (population 480,577, 55.9% non-Hispanic white and 26.2% Hispanic). Cases were prospectively collected over the period from October 1, 1988 to September 30, 1990 through pulmonary physicians and primary care physicians. The median age of incident cases was 69 years. People with ILD most often suffered from pulmonary fibrosis or idiopathic pulmonary fibrosis (IPF). The overall crude incidence of all ILDs was 31.5/100,000 person-years in males and 26.1/100,000 person-years in females. The publication pre-dates the ATS/ERS classification consensus (American Thoracic Society and the European Respiratory Society, 2002) and hence does not report incidence of idiopathic interstitial pneumonia (IIP) as we currently know it. A Danish nationwide retrospective population-based study provided estimates of the incidence of ILD based on 21,765 cases (58% males, median age males 65 years and females 64 years) collected between 1995 and 2005 and obtained from the Danish National Registry of patients (Kornum et al 2008). Data were age-standardized to the 2000 world population, a projection of the world population demographics based on a subset of countries. Crude incidence rates for ILD are summarized here for the period 2001-2005. The overall incidence rate was 42.66/100,000 PY (95% CI: 41.88-43.44). It was 49.56/100,000 PY (95% CI: 48.36-50.76) in males and 35.90/100,000 PY (95% CI: 34.90-36.91) in females. The incidence increased with age, from 16.23/100,000 PY (95% CI: 15.12-17.35) among people aged 0-14 years to 165.41/100,000 PY (95% CI: 157.73-173.08) among people older than 80 years. The incidence rate in people aged 65-79 years was 118.02/100,000 PY (95% CI: 114.07-121.98). The publication does not include incidence estimates for the IIP subgroup, but it

Risk	Interstitial lung disease >severity, frequency, and specificity
	does report crude incidence density of IPF – the most frequently occurring IIP – as 5.28 (95% CI: 5.01–5.56) per 100,000 PY. Karakatsani et al (2009) collected data through pulmonologists in Greece to assess the incidence of ILD in 2004. For the classification of idiopathic interstitial pneumonias, guidelines from the ATS/ERS classification consensus were used. The number of cases identified was 967 (mean age 58 years and 53.6% females). The overall annual incidence of ILD in 2004 was estimated to be 4.63/100,000 PY, while incidence of the IIPs was estimated at 1.5/100,000 PY. Of the 285 IIP cases identified, IPF was found to be the most frequently occurring disease entity (n=189, 66% of all IIPs) with an estimated incidence of 0.93/100,000 PY. Lopez-Campos et al (2004) reported an incidence of ILD obtained from a prospective, multicentre population-based registry established in nine provinces in the south of Spain (population of 6,848,243). Data were collected over the 1998-2000 period. Incidence was estimated on the basis of 744 cases identified only by pulmonologists in hospital pulmonology departments. Consequently, reported incidence rates might be underestimated. The crude annual cumulative incidence of all ILDs was estimated to be 3.62/100,000 persons. The mean age at ILD diagnosis was 61 years (Standard deviation 16 years). The male:female ratio for ILD cases was 1.3:1. The crude annual cumulative incidence of the IIPs was estimated to be 1.40/100,000 persons. Xaubet et al (2004) reported results from a registry of incident cases of ILD over one year (Oct 2000- Sept 2001) set up by pulmonary medicine centers in Spain. Twenty-three centers (out of 37 contacted) participated covering a population of 6.7 million people. The centers identified 511 cases of ILD (53.8% male) yielding an estimated annual incidence of ILD of 7.6/100,000 persons. Guidelines from the ATS/ERS classification consensus were used to determine the classification of the IIPs. Among the 511 ILD cases identified, 268 (52.4%) were classified as IIP, yielding an estimated annual incidence of approximately 4.0/100,000 persons. Similar to the above mentioned studies, a potential limitation of this study is that cases diagnosed in medical clinics/departments other than pulmonary medicine centers are not included.
Risk groups or risk factors	Age, Smoking, environmental and occupational toxins, medications, radiation, chemotherapy and increased oxygen.
Potential mechanisms	Unknown.
Preventability	If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
Impact on individual patient	Impact on quality of life in severe cases and if complications occur.
Potential public health impact of safety concern	Unknown.
Evidence source	As cited above.
MedDRA terms	Interstitial Lung Disease (SMQ).

Table 8-6 Important identified risk: Immune-mediated necrotizing myopathy

Risk	Immune-mediated necrotizing myopathy (IMNM)
Frequency with 95%	Data not available

Risk	Immune-mediated necrotizing myopathy (IMNM)
CI	
Seriousness/outcomes	There is no data on the Immune-mediated necrotizing myopathy during specific use of fluvastatin in the literature but latest literature articles focus on IMNM as statins class effect.
Severity and nature of risk	IMNM is described as immune polymyopathy containing myofiber necrosis, regeneration, and a poor mononuclear cell infiltrate with varying trans-sarcolemmal major histocompatibility complex (MHC) class I positivity. As in other immune-mediated necrotizing myopathies, statin-induced myositis is characterised by proximal muscle weakness with marked serum creatinine kinase elevations and histological evidence of myonecrosis, with little or no inflammatory cell infiltration. It may persist despite discontinuation of statin treatment and may need to be treated with immuno-suppressive drugs. Statin-induced necrotizing myositis is increasingly being recognised as part of the “statin-induced myopathy spectrum”.
Background incidence/prevalence	Autoimmune myositis is rare, with an estimated prevalence of 22 in 100,000 and statin-induced autoimmune myositis is rarer still, with a prevalence of 1 in 100,000. There is less of a female preponderance in statin-induced autoimmune myositis, and onset appears to be more common after the age of 50 (Hamann et al 2013).
Risk groups or risk factors	Muscle imbalance, decreased flexibility, overweight, advancing age, sex: female, alignment abnormalities of the leg. Patients who present at younger age (<50 year’s old) of onset of symptoms appear to represent a slightly different subgroup of patients, where despite clinically having symptoms in keeping with a diagnosis of statin-induced autoimmune myositis and the presence of HMGCR antibodies, a history of statin exposure is sometimes lacking. In contrast to patients with a history of statin exposure, this subset is often of African–American descent, possesses a higher serum CK level and responds less well to treatment [Hamann et al (2013)].
Potential mechanisms	Mammen et al (2011) demonstrated a plausible causal link between statin exposure and this distinct form of IMNM through identification of the autoantigen as HMGCR. Unlike other necrotizing myopathies, statin-induced myopathy is associated with the presence of autoantibodies directed against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR, the enzyme target of statin therapies), and with Human Leukocyte Antigen-DRB1*11.
Preventability	Yes, by monitoring patients for unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever.
Impact on individual patient	Impact on quality of life in severe cases and if complications occur.
Potential public health impact of safety concern	Unknown.
Evidence source	As cited above.
MedDRA terms	Immune-mediated necrotizing myopathy (PT).

Table 8-7 Important potential risk: Use during Pregnancy

Risk	Use during Pregnancy
Frequency with 95% CI	Data not available

Risk	Use during Pregnancy
Seriousness/outcomes	There is insufficient data on the use of fluvastatin during pregnancy. Based on preclinical data, it is expected that fluvastatin is excreted into human milk. There is insufficient information on the effects of fluvastatin in newborns / infants. In animal studies no effects on male and female fertility were observed.
Severity and nature of risk	Lescol is contraindicated in pregnancy and in nursing mothers. Women of child bearing age have to use effective contraception. If a patient becomes pregnant while taking lescol, therapy should be discontinued immediately. Like other HMG-CoA reductase inhibitors, lescol decrease the synthesis of cholesterol and possibly other biologically active substances derived from cholesterol. Thus it may cause foetal hard inclusive of foetal malformation. Current SmPC of Lescol is adequatein describing the nature of this risk.
Background incidence/prevalence	The European surveillance of congenital anomalies (EUROCAT) reported for the period 2008-2012 a prevalence rate of 217.1 cases of congenital anomalies (excluding chromosomal) per 10,000 births (including live birth, foetal death and terminations of pregnancy for foetal anomaly following prenatal diagnosis) (EUROCAT 2014). In the US 3,030 infants with birth defects per 100,000 live births were reported by CDC (CDC 2008). Worldwide about 6% of all newborn infants have serious birth defects of genetic or partially genetic origin and the annual prevalence of congenital malformations was 3,650 per 100,000 births (Christianson et al 2006).
Risk groups or risk factors	Non-use of contraceptive measures.
Potential mechanisms	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.
Preventability	Yes, Lescol/Lescol XL is contraindicated in breastfeeding women. Lescol/Lescol XL is contraindicated during pregnancy.
Impact on individual patient	Impact on quality of life in severe cases and if complications occur.
Potential public health impact of safety concern	Unknown.
Evidence source	As cited above.
MedDRA terms	Pregnancy and neonatal topics (SMQ).

Table 8-8 Important potential risk: Tendinopathy

Risk	Tendinopathy
Frequency with 95% CI	Data not available.
Seriousness/outcomes	Tendinpathies such as tendinitis, tears and complete ruptures.
Severity and nature of risk	The exact etiology of tendinopathies has not been fully elucidated and different stresses may induce varying responses. There are multifactorial theories such as tensile overload, tenocyte related collagen synthesis disruption, tendon load induced ischemia, neural sprouting, thermal damage, and histological adaptive compressive responses seen as some of the causative factors that give rise to activity disruption and disability due to tendinopathies.

Risk	Tendinopathy
Background incidence/prevalence	There are no data on incidence and prevalence of tendinopathy in the non-exposed general population. Population based data are scarce, many studies are based on reports from outpatient or accident and emergency departments, sports injuries, and mostly focused on Achilles tendinopathy. De Jonge et al (2011) reported an incidence rate of Achilles tendinopathy of 1.85 per 1,000 and a prevalence of 2.01 per 1,000 Dutch general practice registered patients in 2009 (52.3% [95%CI 42.7 to 62.0] of cases occurred in women). The overall incidence rate in the adult population 21-60 years was 2.35 per 1,000. Population baseline incident rates have been determined in few studies in order to place in context the occurrence of specific drug-related tendinopathy. Sode et al (2007) reported the Incidence rate of Achilles tendon rupture in Funen County (Denmark) in the period 1991–2002. The mean incidence rate was 27.3 cases/100,000 person-years, but there was a trend towards an increased incidence during this period – from 22.1/100,000 person-years in 1991 to 32.6/100,000 person-years in 2002. The peak incidence rate was found among persons aged 30–49 years (55/100,000 persons per year). In a UK general practice population (1986-2009), the baseline incidence of Achilles tendonitis and tendon rupture was 92 and 24 per 100,000 person-years, respectively. Among subjects with Achilles tendonitis, 46.5% were women, 73.7% were aged less than 60 years. Among subjects with tendon rupture, 31.9% were women, 57.7% were aged less than 60 years (Wise et al 2012). In a US cohort of patients from a health insurer claims database (1997-2001), there were 947 cases of Achilles tendon rupture in 9 832 971 person-years of experience in the cohort, yielding a crude incidence rate of 1.0 per 10,000 person-years (95%CI 0.9–1.1) (Seeger et al 2006).
Risk groups or risk factors	Muscle imbalance, decreased flexibility, overweight, advancing age, sex: female, alignment abnormalities of the leg.
Potential mechanisms	Unknown.
Preventability	Yes, If pain is experienced, early treatment is recommended to prevent serious injury from occurring.
Impact on individual patient	Impact on quality of life in severe cases and if complications occur.
Potential public health impact of safety concern	Unknown.
Evidence source	As cited above.
MedDRA terms	Tendon Disorders (HLT).

8.4 Part II Module SVII.4. Identified and potential interactions

8.4.1 Part II Module SVII.4.1 Overview of potential for interactions

Fluvastatin is mainly metabolized in the liver. There are multiple, alternative cytochrome P450 (CYP450) pathways for fluvastatin biotransformation and thus fluvastatin metabolism are relatively insensitive to CYP450 inhibition, a major cause of adverse drug-drug interactions.

Fluvastatin inhibited only the metabolism of compounds that are metabolized by CYP2C9. Despite the potential that therefore exists for competitive interaction between fluvastatin and compounds that are CYP2C9 substrates, such as diclofenac, phenytoin, tolbutamide, and warfarin, clinical data indicate that this interaction is unlikely. Concomitant administration of drugs known to induce the activity of CYP2C9 may decrease the plasma levels of tizanidine. The decreased plasma levels of fluvastatin may reduce the therapeutic effect of Lescol.

8.4.2 Part II Module SVII.4.2 Important identified and potential interactions

Table 8-9 Important identified interaction: Strong CYP 2C9 inhibitor (fluconazole)

Interacting substance	Strong CYP 2C9 inhibitor (fluconazole)
Effect of interaction	Administration of fluvastatin to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor) resulted in an increase in the AUC and C_{max} of fluvastatin by about 84% and 44% respectively.
Evidence source	Well-documented literature data.
Possible mechanisms	Fluvastatin metabolism is governed mainly by CYP2C9.
Potential health risk	Low.
Discussion	Although there was no clinical evidence that the safety profile of fluvastatin was altered in patents pre-treated with fluconazole for 4 days, the possibility of increase in fluvastatin plasma exposure cannot be ruled out. Therefore, caution should be exercised when fluvastatin is administered concomitantly with fluconazole.

Table 8-10 Important identified interaction: Strong CYP 2C9 inducer (rifampicin)

Interacting substance	Strong CYP 2C9 inducer (rifampicin)
Effect of interaction	Administration of fluvastatin to healthy volunteers pre-treated with rifampicin (rifampin) resulted in a reduction of the bioavailability of fluvastatin by about 50%.
Evidence source	Well-documented internal clinical study reports.
Possible mechanisms	Fluvastatin metabolism is governed mainly by CYP2C9.
Potential health risk	Low.
Discussion	Although 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.

Table 8-11 Important identified interaction: Coumarin derivatives (warfarin)

Interacting substances	Coumarin derivatives (warfarin)
Effect of interaction	In healthy subjects, 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.
Evidence source	Well-documented internal clinical study reports and literature.
Possible mechanisms	Fluvastatin and Warfarin metabolism are governed mainly by CYP2C9.

Interacting substances	Coumarin derivatives (warfarin) Fluvastatin is a weak inhibitor of CYP2C9, by which S-warfarin (which has greater anticoagulant activity than R-warfarin) is metabolized.
Potential health risk	Low.
Discussion	There are case reports on bleeding episodes and/or increased prothrombin times in patients on concomitant therapy with fluvastatin and warfarin or other coumarin derivatives. Therefore, it is recommended that prothrombin times have to be monitored when fluvastatin treatment is initiated, discontinued, or the dosage changed in patients receiving warfarin or other coumarin derivatives.

Table 8-12 Important identified interaction: Anti-diabetic drugs (glibenclamide)

Interacting substances	Anti-diabetic drugs (glibenclamide)
Effect of interaction	In glibenclamide-treated NIDDM patients (n=32), administration of fluvastatin (40 mg twice daily for 14 days) increased the mean C_{max}, AUC, and t1/2 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. However there were no changes in glucose, insulin and C-peptide levels.
Evidence source	Well-documented internal clinical study report.
Possible mechanisms	The changes in the pharmacokinetics of glibenclamide (glyburide) caused by fluvastatin are not understood.
Potential health risk	Low.
Discussion	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.

Table 8-13 Important potential interaction: Pharmacodynamic interaction with colchicine

Interacting substance	Colchicine.
Effect of interaction	Concomitant administration of fluvastatin with colchicine can cause myotoxicity and rhabdomyolysis.
Evidence source	Literature data.
Possible mechanisms	Additive or synergistic effect.
Potential health risk	High.
Discussion	Lescol/Lescol XL should be used with caution in patients receiving colchicine as concomitant medication due to the increased risk of myotoxicity, including muscle pain and weakness and rhabdomyolysis.

Table 8-14 Important potential interaction: Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin)

Interacting substances	Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin).
Effect of interaction	Increased risk of myopathy has been observed in patients receiving these interacting drugs with other HMG-CoA reductase inhibitors.
Evidence source	Well-documented internal safety report and literature data.
Possible mechanisms	Additive or synergistic effect.

Interacting substances	Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin).
Potential health risk	High.
Discussion	The risk of myopathy has been reported to be increased in patients receiving immunosuppressive drugs (including cyclosporin), 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 cyclosporin, myopathy has not been observed. Isolated cases of myopathy have been reported post marketing for concomitant administration of fluvastatin with cyclosporin and fluvastatin with colchicine. Therefore, Lescol/Lescol XL should be used with caution in patients receiving these concomitant medications.

8.5 Part II Module SVII.5. Pharmacological class effects

8.5.1 Part II Module SVII.5.1 Pharmacological class risks already included as important identified or potential risks

Rhabdomyolysis

Published data on the epidemiology of rhabdomyolysis are scarce. The exact incidence is difficult to establish, because different case definitions have been used, and until 2006 there was no a specific diagnostic code for the disease. Rhabdomyolysis seems to be very rare. In a retrospective population-based analysis using the UK-based General Practice Research Database, only 25 patients out of 2.5 million in a base population of patient aged 20-75 years were found to have rhabdomyolysis between 1990 and 1999 (Black and Jick 2002). However, this number is very likely to be underestimated because some possible cases of rhabdomyolysis might not have been identified (Black and Jick 2002). Based on a cohort study performed in the Kaiser Permanente Northwest HMO database, Nichols and Koro (2007) reported incidence rates of rhabdomyolysis of 10 per 100,000 person-year in non-diabetic general population, with no significant differences between statin exposed and non-exposed subjects. The Armed Forces Health Surveilance Center (2011) reported that in 2010 there were 358 incident cases of rhabdomyolysis likely due to physical exertion and/or heat stress ("exertional rhabdomyolysis") among the US Armed Forces, with the crude incidence rate of 24.5 per 100,000 person-years, while Hill et al (2011) reported an annual incidence of 7 to 8 per 10,000 soldier population in the US Active Duty Army between 2003 and 2006.

Most information on the incidence of rhabdomyolysis comes from observational studies in users of statins. In a recent systematic review of cohort studies, the incidence of rhabdomyolysis in statin users was reported to be 11 per 100,000 person-years if all statins were considered, it was 3.4 (95% CI 1.6-6.5) per 100,000 person-years among all statin users except cerivastatin (the latter had an incidence of 46 (95% CI 13-120) per 100,000 person years (Law & Rudnicka 2006). The incidence again was 10 times higher if a fibrate such as gemfibrozil was used in combination with statins. Similar results were found by (Graham et al 2004) who estimated the risk of rhabdomyolysis in patients treated with lipid-lowering drugs (including statins) in the ambulatory setting using claims data from 11 managed care health plans across the United States. Average incidence rate for rhabdomyolysis with statin monotherapy (atorvastatin, pravastatin, or simvastatin) was about 4.4 (95% CI 2.0-8.4), for

cerivastatin was 53.4 (95% CI 14.6-136.8), and for fibrates it was 28.2 (95% CI 5.8-82.4) per 100,000 person-years. This rate increased to about 60 per 100,000 for combination therapy of statins with a fibrate. The recent publication (Floyd et al 2012), reported the incidence rates in all statin users of 10.1 per 100,000 person-years (95% CI: 7.8 -14.5) according to a population-based study using computerized pharmacy data and electronic medical records for enrollees of Group Health Cooperative from January 2006 through December 2010. Common etiologies for rhabdomyolysis other than statin use included prolonged immobility, arterial ischemia, recent surgery, and severe infection.

Immune-mediated necrotizing myopathy

In recent years, several reports have described patients suspected of having developed statin-associated autoimmune myopathies. A case series by Needham et al 2007 reported the development of autoimmune necrotizing myopathy in several patients with a history of statin use. These patients developed progressive weakness and elevated creatine kinase levels. In contrast to those with self-limited statin myopathy, the symptoms of patients with autoimmune necrotizing myopathy did not improve after discontinuation of statins.

In another study (Grable-Esposito et al 2010), investigators reported similar findings in a larger group of statin-exposed patients. Muscle biopsy in these patients showed myofiber degeneration, necrosis and regeneration with minimal inflammation; these muscle biopsy features define a necrotizing myopathy. Again, the clinical picture of myositis persisted despite statin discontinuation and required immunosuppressive therapy to achieve clinical improvement. The association with statin use was confirmed when the investigators noted a much higher prevalence of statin use in these patients than that of other inflammatory myopathies such as dermatomyositis, polymyositis and inclusion body myositis (IBM).

In parallel, a group of investigators (Christopher-Stine et al 2010) at the Johns Hopkins Myositis Center identified a previously unknown autoantibody in patients with autoimmune necrotizing myopathy. This novel autoantibody recognized a then unknown protein target that migrated as a doublet with molecular weights of 200 and 100 kDa. Interestingly, they noted a high prevalence of statin use in this anti-200/100 antibody-positive cohort, especially when compared with age-matched individuals with other inflammatory myopathies such as dermatomyositis, polymyositis and IBM. Again, the myopathic process in this group did not resolve after discontinuation of statins.

After further investigation, the anti-200/100 autoantibody was found to be directed against the catalytic domain of HMGCR, the pharmacologic target of statins. As statins upregulate HMGCR protein levels, this suggests a mechanistic link between statin use and the development of autoantibodies against this protein.

To better characterize the association between the anti-HMGCR antibody and statin exposure, the investigators used an ELISA to screen serum samples from 750 patients referred to their myositis centre with suspected myopathy. Myopathy was suspected on the basis of proximal muscle weakness, elevated creatine kinase levels, electrophysiologic testing suggestive of myopathy and, where available, muscle MRI and/or muscle biopsies. The investigators found that 6% of all patients in the cohort with suspected myopathy tested positive for anti-HMGCR antibody. Confirming their suspicion, two-thirds of these patients had a history of statin

exposure. This correlation was more impressive in anti-HMGCR positive individuals older than 50 years of age, in whom 92% had statin exposure (Mammen et al 2011).

Although the epidemiologic characteristics of anti-HMGCR myopathy are not fully known, the incidence is estimated to be roughly two per million per year. Among those with autoimmune myopathy, however, anti-HMGCR myopathy is not rare; 6% of myositis patients seen at the Johns Hopkins Myositis Center prior to publication of these findings (and subsequent referral bias) had these antibodies. Moreover, nearly one-third of those with necrotizing myopathies were anti-HMGCR positive (Mohassel et al 2013).

Tendinopathy

Drug-induced tendon toxicity is rare but often underestimated. To date, four main drug classes have been incriminated in tendinopathies. Quinolones and long-term glucocorticoids are the most widely known, but statins and aromatase inhibitors can also induce tendon damage. The specific pathophysiological mechanisms responsible for drug-induced tendinopathies remain unknown. Proven risk factors have been identified, such as age older than 60 years, pre-existing tendinopathy, and potentiation of toxic effects when several drug classes are used in combination. Mean time to symptom onset varies from a few days with quinolones to several months with statins and several years for long-term glucocorticoid therapy. The most common sites of involvement are the lower limb tendons, most notably the body of the Achilles tendon (Kirchgesner et al 2014).

Marie et al 2008 suggests that tendon impairments might be another side effect associated with the use of statins. They stress, however, that statin-associated tendon impairments are extremely rare, and none have been reported in pre- and post-marketing studies, including all the large statin trials. Anecdotal reports, however, have been described in the literature. With the anecdotal evidence in mind, the group retrospectively sought to identify all tendinous disorders attributable to statin therapy over a 15-year period. From 1990 to 2005, 96 spontaneous reports of tendon complications were reported to 31 French Pharmacovigilance Centers. The average age of those who experienced problems was 56 years. The median time to onset of the side effect was 243 days, although complications arose in one patient within 24 hours of taking the statin. Nearly one-third of those experiencing tendon complications had an associated condition that favored the onset of tendon side effects, such as diabetes, hyperuricemia, and participation in sports. The most common complication was tendonitis, followed by tendonitis with tendon rupture and de novo tendon rupture. Marie and colleagues noted that complications were serious enough for 17 patients to report to a hospital, and 19 patients had significant functional difficulties, such as problems walking, decreased flexion, bruising, and pain. The researchers write that the tendon disorders could be reasonably attributed to statin therapy because "there was a temporal relationship between onset of tendinous signs and the initiation of statin therapy." The problems cleared up or improved after stopping the drugs and recurred in seven patients who were restarted on statins. The authors noted that the side effects occurred with all the statins—atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin—but that there is no known reason why the drugs might produce these injuries.

Cases of tendonitis and tendon ruptures have been associated with the use of statins (Marie et al 2009). These complications are observed in tendons in different sites, for example, the

distal biceps tendon, the patellar tendon, the quadriceps tendon and the Achilles tendon which seems to be more affected by injuries.

8.5.2 Part II Module SVII.5.2 Important pharmacological class effects not discussed above

None.

9 Part II Safety Specification Module SVIII: Summary of the safety concerns

Table 9-1 Summary of safety concerns

Important identified risks	Severe hepatic disorder Hypersensitivity (rash, urticaria)/ angioedema/anaphylaxis Rhabdomyolysis New onset diabetes Mellitus Interstitial lung disease Immune-mediated necrotising myopathy Drug-drug interactions, with • Strong CYP 2C9 inhibitor (fluconazole) • Strong CYP 2C9 inducer (rifampicin) • Coumarin derivatives (warfarin) • Anti-diabetic drugs (glibenclamide)
Important potential risks	Use during Pregnancy Tendinopathy Drug-drug interaction, with • Pharmacodynamic interaction with colchicine • Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin)
Missing information	Use in paediatric patients < 9 years of age Use during lactation

10 Part III: Pharmacovigilance Plan

10.1 Part III.1. Safety concerns and overview of planned pharmacovigilance actions

Table 10-1 Important identified risk: Severe hepatic disorder

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To closely monitor, evaluate and further characterize symptoms of this risk. To monitor for greater severity, frequency, and specificity. To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)

Table 10-2 Important identified risk: Hypersensitivity (rash, urticaria)/ angioedema/anaphylaxis

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None.	Routine Pharmacovigilance	To closely monitor, evaluate and further characterize symptoms of this risk. To monitor for greater severity, frequency, and specificity. To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)

Table 10-3 Important identified risk: Rhabdomyolysis

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To closely monitor, evaluate and

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
		further characterize symptoms of this risk. To monitor for greater severity, frequency, and specificity. To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)

Table 10-4 Important identified risk: New onset diabetes mellitus

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To closely monitor, evaluate and further characterize symptoms of this risk. To monitor for greater severity, frequency, and specificity. To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)

Table 10-5 Important identified risk: Interstitial lung disease

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To closely monitor, evaluate and further characterize symptoms of this risk. To monitor for greater severity, frequency, and specificity. To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
		• Risk factors • Characteristics of exposure (dose, duration, co-medications)

Table 10-6 Important identified risk: Immune-mediated necrotizing myopathy

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To closely monitor, evaluate and further characterize symptoms of this risk. To monitor for greater severity, frequency, and specificity. To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)

Table 10-7 Important identified interaction: Strong CYP 2C9 inhibitor (fluconazole)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Monitoring of the frequency, severity, and clinical consequences of this drug-drug interaction.	Routine Pharmacovigilance	Assess the magnitude and confirm the relevance of this interaction in the fluvastatin treated population.

Table 10-8 Important identified interaction: Strong CYP 2C9 inducer (rifampicin)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Monitoring of the frequency, severity, and clinical consequences of this drug-drug interaction.	Routine Pharmacovigilance	Assess the magnitude and confirm the relevance of this interaction in the fluvastatin treated population.

Table 10-9 Important identified interaction: Coumarin derivatives (warfarin)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Monitoring of the frequency, severity, and clinical consequences of this drug-drug interaction.	Routine Pharmacovigilance	Assess the magnitude and confirm the relevance of this interaction in the fluvastatin treated population.

Table 10-10 Important identified interaction: Anti-diabetic drugs (glibenclamide)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Monitoring of the frequency, severity, and clinical consequences of this drug-drug interaction.	Routine Pharmacovigilance	Assess the magnitude and confirm the relevance of this interaction in the fluvastatin treated population.

Table 10-11 Important potential risk: Use during Pregnancy

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To closely monitor, evaluate and further characterize symptoms of this risk. To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)

Table 10-12 Important potential risk: Tendinopathy

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine Pharmacovigilance	To closely monitor, evaluate and further characterize symptoms of this risk. To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)

Table 10-13 Important potential interaction: Pharmacodynamic interaction with colchicine

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Monitoring of the frequency, severity, and clinical consequences of this drug-drug interaction.	Routine Pharmacovigilance	Assess the magnitude and confirm the relevance of this interaction in the fluvastatin treated population.

Table 10-14 Important potential interaction: Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Monitoring of the frequency, severity, and clinical consequences of these drug-drug interactions: bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin.	Routine Pharmacovigilance	Assess the magnitude and confirm the relevance of these interactions in the fluvastatin treated population.

Table 10-15 Important missing information: Use in paediatric patients <9 years of age

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Monitor risk associated with fluvastatin use in paediatric patients<9 years of age.	Routine Pharmacovigilance	Monitor risk associated with fluvastatin use in paediatric patients<9 years of age in post-marketing setting with a large exposure

Table 10-16 Important missing information: Use during lactation

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Monitor risk associated with fluvastatin use during lactation	Routine Pharmacovigilance	Monitor risk associated with fluvastatin use in post-marketing setting with a large exposure.

10.2 Part III.2. Additional pharmacovigilance activities to assess effectiveness of risk minimization measures

No additional pharmacovigilance activities are planned.

10.3 Part III.3. Studies and other activities completed since last update of Pharmacovigilance Plan

This section is not applicable as this is the first RMP for fluvastatin.

10.4 Part III.4. Details of outstanding additional pharmacovigilance activities

There are no outstanding additional PhV activities for fluvastatin.

10.4.1 Part III.4.1. Imposed mandatory additional pharmacovigilance activity (key to benefit/risk)

Table 10-17 Imposed activities considered key to the benefit risk of the product.

	Description of activity (or study title if known)	Milestone	Due Date
1	Not applicable.		

10.4.2 Part III.4.2. Mandatory additional PhV Activity (being a specific obligation)

Table 10-18 Specific obligations

	Description of activity (or study title if known)	Milestone	Due Date
1	Not applicable.		

10.4.3 Part III.4.3. Required additional pharmacovigilance activities to address specific safety concerns or to measure effectiveness of risk minimization measures

Table 10-19 Required additional pharmacovigilance activities

	Description of activity (or study title if known)	Milestone	Due Date
1	Not applicable.		

10.4.4 Part III.4.4. Stated additional pharmacovigilance activities

Table 10-20 Stated additional pharmacovigilance activities

	Description of activity (or study title if known)	Expected date of report
1	Not applicable.	

10.5 Part III.5. Summary of the Pharmacovigilance Plan

10.5.1 Part III.5.1. On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

There are no additional PhV activities are ongoing or planned for fluvastatin.

Table 10-21 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final Reports (planned or actual)

Study/activity	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final Reports (planned or actual)
Not applicable.				

10.5.2 Part III.5.2. Table of completed studies/activities from the Pharmacovigilance Plan

There are no additional PhV activities completed for fluvastatin.

Table 10-22 Completed studies from the Pharmacovigilance Plan

Study/activity	Objectives	Safety concerns addressed	Status (Completed)	Date for Submission of final reports (Planned or Actual)
Not applicable.				

11 Part IV: Plans for post-authorization efficacy studies

Fluvastatin and other members of the statin class of HMG-CoA reductase inhibitors have been widely studied globally and used extensively over the last 20 years. Within the clinical trial program (including phase 4 studies) no patient groups have been identified which do not respond to fluvastatin. Furthermore for the statin class of medications there is no evidence for specific populations with altered responses except for theoretical considerations of specific genetic disorders impacting the LDL-cholesterol receptor which may have no response to statin medications.

12 Part V: Risk minimization measures

12.1 Part V.1. Risk minimization measures by safety concern

Table 12-1 Risk minimization measures by safety concern: Severe hepatic disorder

Safety concern	Severe hepatic disorder
Objectives of the risk minimization measures	To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors Characteristics of exposure (dose, duration, co-medications)
Routine risk minimization measures	SmPC Section 4.3 (Contraindication). SmPC Section 4.4 (Special warnings and precautions for use).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None.
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-2 Risk minimization measures by safety concern: Hypersensitivity (rash, urticaria)/ angioedema/anaphylaxis

Safety concern	Hypersensitivity (rash, urticaria)/ angioedema/ anaphylaxis
Objectives of the risk minimization measures	To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors)

Safety concern	Hypersensitivity (rash, urticaria)/ angioedema/ anaphylaxis
	• Risk factors • Characteristics of exposure (dose, duration, co-medications)
Routine risk minimization measures	SmPC Section 4.3 (Contraindication): Rash and urticaria are mentioned in the ADR section of the SmPC (Section 4.8).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None.
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not Applicable.
Comment	None.

Table 12-3 Risk minimization measures by safety concern: Rhabdomyolysis

Safety concern	Rhabdomyolysis
Objectives of the risk minimization measures	To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)
Routine risk minimization measures	SmPC Section 4.4 (Special warnings and precautions for use).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None.
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.

Safety concern	Rhabdomyolysis
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not Applicable.
Impact of risk minimization	Not Applicable.
Comment	None.

Table 12-4 Risk minimization measures by safety concern: New onset diabetes mellitus

Safety concern	New onset diabetes mellitus
Objectives of the risk minimization measures	To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)
Routine risk minimization measures	SmPC Section 4.4 (Special warnings and precautions for use).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None.
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.

Safety concern	New onset diabetes mellitus
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-5 Risk minimization measures by safety concern: Interstitial lung disease

Safety concern	Interstitial lung disease
Objectives of the risk minimization measures	To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)
Routine risk minimization measures	SmPC Section 4.4 (Special warnings and precautions for use).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None.
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-6 Risk minimization measures by safety concern: Immune-mediated necrotizing myopathy

Safety concern	Immune-mediated necrotizing myopathy
Objectives of the risk minimization measures	To identify and/or characterize the following: • Clinical characteristics of the events

Safety concern	Immune-mediated necrotizing myopathy
	• Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)
Routine risk minimization measures	SmPC Section 4.4 (Special warnings and precautions for use). SmPC Section 4.8: SOC Musculoskeletal and connective tissue disorders, "Frequency Not known: immune-mediated necrotizing myopathy".
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-7 Risk minimization measures by safety concern: Interaction with strong CYP 2C9 inhibitor (fluconazole)

Safety concern	Interaction with strong CYP 2C9 inhibitor (fluconazole)
Objectives of the risk minimization measures	To caution against the risk of an increase in the AUC and C_{max} of fluvastatin by about 84% and 44%, respectively, when administered to healthy volunteers pre-treated with fluconazole (CYP 2C9 inhibitor).
Routine risk minimization measures	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	

Safety concern	Interaction with strong CYP 2C9 inhibitor (fluconazole)
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-8 Risk minimization measures by safety concern: Interaction with strong CYP 2C9 inducer (rifampicin)

Safety concern	Interaction with strong CYP 2C9 inducer (rifampicin)
Objectives of the risk minimization measures	To caution against the risk of a reduction of the bioavailability of fluvastatin by about 50% when administered to healthy volunteers pre-treated with rifampicin (rifampin).
Routine risk minimization measures	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.

Safety concern	Interaction with strong CYP 2C9 inducer (rifampicin)
Comment	None.

Table 12-9 Risk minimization measures by safety concern: Interaction with coumarin derivatives (warfarin)

Safety concern	Interaction with coumarin derivatives (warfarin)
Objectives of the risk minimization measures	To caution against the risk of bleeding episodes and/or increased prothrombin times.
Routine risk minimization measures	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-10 Risk minimization measures by safety concern: Interaction with anti-diabetic drug (glibenclamide)

Safety concern	Interaction with anti-diabetic drug (gligenclamide)
Objectives of the risk minimization measures	To caution against the risk of increased mean C_{max}, AUC, and $t_{1/2}$ of glibenclamide approximately 50%, 69% and 121%, respectively, in glibenclamide-treated NIDDM patients (n=32), when administered fluvastatin (40 mg twice daily for 14 days).
Routine risk minimization measures	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk	None

Safety concern	Interaction with anti-diabetic drug (gligenclamide)
minimization measures	
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-11 Risk minimization measures by safety concern: Use during Pregnancy

Safety concern	Use during Pregnancy
Objectives of the risk minimization measures	• • To minimize the risk to women during pregnancy.
Routine risk minimization measures	SmPC Section 4.6 (Fertility, pregnancy, and lactation).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None.
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness	Not applicable.

Safety concern	Use during Pregnancy
measurement	
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-12 Risk minimization measures by safety concern: Tendinopathy

Safety concern	Tendinopathy
Objectives of the risk minimization measures	To identify and/or characterize the following: • Clinical characteristics of the events • Types of patients at risk (demographic factors) • Risk factors • Characteristics of exposure (dose, duration, co-medications)
Routine risk minimization measures	SmPC section 4.8: "Tendinopathy, sometimes complicated by tendon rupture" has been reported with other statins.
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None.
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-13 Risk minimization measures by safety concern: Pharmacodynamic interaction with colchicine

Safety concern	Pharmacodynamic interaction with colchicine
Objectives of the risk minimization measures	To caution against concomitant administration of fluvastatin with colchicine which can cause myotoxicity and rhabdomyolysis.
Routine risk	SmPC Section 4.5 (Interaction with other medicinal products and other

Safety concern	Pharmacodynamic interaction with colchicine
minimization measures	forms of interaction).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-14 Risk minimization measures by safety concern: Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin)

Safety concern	Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin).
Objectives of the risk minimization measures	To caution against the increased risk of myopathy that has been observed in patients receiving these interacting drugs with other HMG-CoA reductase inhibitors.
Routine risk minimization measures	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.

Safety concern	Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin).
concern will be measured	
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-15 Risk minimization measures by safety concern: Use in paediatric patients < 9 years of age

Safety concern	Use in paediatric patients < 9 years of age
Objectives of the risk minimization measures	To clarify that there is a lack of information on the use in pediatric patients < 9 years of age.
Routine risk minimization measures	SmPC Section 4.4 (Special warnings and precautions for use).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None.
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

Table 12-16 Risk minimization measures by safety concern: Use during lactation

Safety concern	Use during lactation
Objectives of the risk minimization measures	To clarify that there is a lack of information on the use during lactation.
Routine risk minimization measures	SmPC Section 4.6 (Fertility, pregnancy, and lactation).
Comment (e.g. on any differences between SmPCs)	Not applicable.
Other routine risk minimization measures	None.
Additional risk minimization measure	Objective and justification of why needed: Not applicable. Proposed actions/components and rationale: Not applicable.
Effectiveness of risk minimization measures	
How effectiveness of risk minimization measures for the safety concern will be measured	The risks will be monitored in Novartis signal detection system and in the Lescol PSUR's.
Criteria for judging the success of the proposed risk minimization measures	The MAH will assess the effectiveness of the recommended Risk Management Plan (RMP) measure by assessment of data collected through all post-marketing sources.
Planned dates for assessment	Routine assessment of individual case reports, aggregate analysis and PSURs.
Results of effectiveness measurement	Not applicable.
Impact of risk minimization	Not applicable.
Comment	None.

12.2 Part V.2. Risk minimization measure failure (if applicable)

Not applicable.

12.2.1 Part V.2.1. Analysis of risk minimization measure failure

Not applicable.

12.2.2 Part V.2.2 Revised proposal for risk minimization

Not applicable.

12.3 Part V.3. Summary table of risk minimization measures

Table 12-17 Summary table of Risk Minimization Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Severe hepatic disorder	SmPC Section 4.3 (Contraindication):	Not applicable.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Lescol/Lescol XL is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see SmPC Sections 4.2, 4.4 and 4.8). SmPC Section 4.4 (Special warnings and precautions for use): Post marketing cases of fatal and non-fatal hepatic failures have been reported with some statins including Lescol/Lescol XL. Although a causal relationship with Lescol/Lescol XL treatment has not been determined, patients should be advised to report any potential symptoms or signs of hepatic failure (e.g. nausea, vomiting, loss of appetite, jaundice, impaired brain function, easy bruising or bleeding), and treatment discontinuation should be considered. As with other lipid-lowering agents, 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. Should an increase in aspartate aminotransferase or alanine aminotransferase 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 Lescol/Lescol XL is administered to patients with a history of liver disease or heavy alcohol ingestion.	
Hypersensitivity (rash, urticaria)/ angioedema/anaphylaxis	SmPC Section 4.3 (Contraindication): Lescol/Lescol XL is contraindicated in patients with known hypersensitivity to fluvastatin or any of the excipients listed in SmPC Section 6.1. Rash, urticaria, and anaphylactic reaction are mentioned in the ADR section of the SmPC.	Not applicable.
Rhabdomyolysis	SmPC Section 4.4 (Special warnings and precautions for use): Myopathy has rarely been reported with fluvastatin. 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	Not applicable.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	therefore be advised to promptly report unexplained muscle pain, muscle tenderness or muscle weakness, particularly if accompanied by malaise or fever. There is no current evidence to require routine monitoring of plasma total CK or other muscle enzyme levels in asymptomatic patients on statins. If CK 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.	
New onset diabetes mellitus	SmPC Section 4.4 (Special warnings and precautions for use): Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.	Not applicable.
Interstitial lung disease	SmPC Section 4.4 (Special warnings and precautions for use): Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see SmPC Section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.	Not applicable.
Immune-mediated necrotizing myopathy	SmPC Section 4.4 (Special warnings and precautions for use): There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment. SmPC Section 4.8: SOC Musculoskeletal and connective tissue disorders, “Frequency Not known: immune-mediated necrotizing	Not applicable

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	myopathy".	
Interaction with strong CYP 2C9 inhibitor (fluconazole)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): 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.	Not applicable
Interaction with strong CYP 2C9 inducer (rifampicin)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): 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.	Not applicable
Interaction with coumarin derivatives (warfarin)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): 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 changes in patients receiving warfarin or other coumarin derivatives.	Not applicable
Interaction with anti-diabetic drug (glibenclamide)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): For patients receiving oral sulfonylureas (glibenclamide [glyburide], tolbutamide) for the treatment of non-insulin-dependent (type 2)	Not applicable

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	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 Cmax, AUC, and t½ of glibenclamide by approximately 50%, 69%, and 121%, respectively. Glibenclamide (5 to 20 mg daily) increased the mean Cmax 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.	
Use during pregnancy	SmPC Section 4.6 (Fertility, pregnancy, and lactation): There is insufficient data on the use of fluvastatin during pregnancy. 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. Therefore, Lescol/Lescol XL is contraindicated during pregnancy (see SmPC Section 4.3).	Not applicable.
Tendinopathy	SmPC section 4.8: “Tendinopathy, sometimes complicated by tendon rupture” has been reported with other statins.	Not applicable.
Pharmacodynemic interaction with colchicine	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): Myotoxicity, including muscle pain and weakness and rhabdomyolysis, has been reported in isolated cases with concomitant administration of colchicines. The benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution	Not applicable
Pharmacodynamic interaction with other drugs (Bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): 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. Since an increased risk of	Not applicable

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	myopathy and/or rhabdomyolysis has been observed in patients receiving HMGCoA reductase inhibitors together with any of these molecules, the benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution 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. 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 in which Lescol XL tablets (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 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 maintenance dose of fluvastatin should be as low as possible when combined with ciclosporin.	
Use in paediatric patients <9 years of age	SmPC Section 4.4 (Special warnings and precautions for use): Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia. 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.	Not applicable.
Use during lactation	SmPC Section 4.6 (Fertility, pregnancy, and lactation) Based on preclinical data, it is expected that fluvastatin is excreted into human milk. There is insufficient information on the effects of fluvastatin in newborns / infants.	Not applicable

13 Part VI: Summary of activities in the risk management plan by product

13.1 Part VI.1 Elements for summary tables in the EPAR

Table 13-1 Part VI.1.1 Summary table of safety concerns

Important identified risks	Severe hepatic disorder Hypersensitivity (rash, urticaria)/angioedema/anaphylaxis Rhabdomyolysis New onset diabetes mellitus Interstitial lung disease Immune-mediated necrotizing myopathy Drug-drug interactions • Strong CYP 2C9 inhibitor (fluconazole) • Strong CYP 2C9 inducer (rifampicin) • Coumarin derivatives (warfarin) • Anti-diabetic drugs (glibenclamide)
Important potential risks	Use during Pregnancy Tendinopathy Drug-drug interaction, with • Pharmacodynamic interaction with colchicine • Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin)
Missing information	Use in paediatric patients < 9 years of age Use during lactation

Table 13-2 Part VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Not applicable.				

Table 13-3 Part VI.1.3 Summary of Post authorization efficacy development plan

Study (type and study number)	Objectives	Efficacy uncertainties addressed	Status	Date for submission of interim or final reports
Not applicable.				

Table 13-4 Part VI.1.4 Summary table of risk minimization measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Severe hepatic disorder	SmPC Section 4.3 (Contraindication): Lescol/Lescol XL is contraindicated in patients with active liver disease, or unexplained, persistent elevations in serum transaminases (see SmPC Sections 4.2, 4.4 and 4.8). SmPC Section 4.4 (Special warnings and precautions for use): Post marketing cases of fatal and non-fatal hepatic failures have been reported with some statins including Lescol/Lescol XL. Although a causal relationship with Lescol/Lescol XL treatment has not been determined, patients should be advised to report any potential symptoms or signs of hepatic failure (e.g. nausea, vomiting, loss of appetite, jaundice, impaired brain function, easy bruising or bleeding), and treatment discontinuation should be considered. As with other lipid-lowering agents, 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. Should an increase in aspartate aminotransferase or alanine aminotransferase 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 Lescol/Lescol XL is administered to patients with a history of liver disease or heavy alcohol ingestion.	Not applicable.
Hypersensitivity (rash, urticaria)/ angioedema/anaphylaxis	SmPC Section 4.3 (Contraindication): Lescol/Lescol XL is contraindicated in patients with known hypersensitivity to fluvastatin or any of the excipients listed in SmPC Section 6.1. Rash and urticaria are mentioned in the ADR section of the SmPC.	Not applicable.
Rhabdomyolysis	SmPC Section 4.4 (Special warnings and precautions for use): Myopathy has rarely been reported with fluvastatin. Myositis and rhabdomyolysis	Not applicable.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	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. There is no current evidence to require routine monitoring of plasma total CK or other muscle enzyme levels in asymptomatic patients on statins. If CK 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.	
New onset diabetes mellitus	SmPC Section 4.4 (Special warnings and precautions for use): Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.	Not applicable.
Interstitial lung disease	SmPC Section 4.4 (Special warnings and precautions for use): Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see SmPC Section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.	Not applicable.
Immune-mediated necrotizing myopathy	SmPC Section 4.4 (Special warnings and precautions for use): There have been rare reports of immune-	Not applicable

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment. SmPC Section 4.8, SOC Musculoskeletal and connective tissue disorders "Not known: immune-mediated necrotizing myopathy".	
Interaction with strong CYP 2C9 inhibitor (fluconazole)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): 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.	Not applicable
Interaction with strong CYP 2C9 inducer (rifampicin)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): 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.	Not applicable
Interaction with coumarin derivatives (warfarin)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): 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	Not applicable

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	concomitant warfarin or other coumarin derivatives. It is recommended that prothrombin times are monitored when fluvastatin treatment is initiated, discontinued, or the dosage changes in patients receiving warfarin or other coumarin derivatives.	
Interaction with anti-diabetic drug (glibenclamide)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): 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 t½ of glibenclamide by 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.	Not applicable
Important potential risks		
Use during Pregnancy	SmPC Section 4.6 (Fertility, pregnancy, and lactation): There is insufficient data on the use of fluvastatin during pregnancy. 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. Therefore, Lescol/Lescol XL is contraindicated during pregnancy (see SmPC Section 4.3).	Not applicable.
Tendinopathy	SmPC section 4.8: “Tendinopathy, sometimes complicated by tendon rupture” has been reported with other statins.	
Pharmacodynamic interaction with colchicine	SmPC Section 4.5 (Interaction with other medicinal products and other forms of	Not applicable

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	interaction): Myotoxicity, including muscle pain and weakness and rhabdomyolysis, has been reported in isolated cases with concomitant administration of colchicines. The benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution	
Pharmacodynamic interaction with other drugs (bezafibrate, gemfibrozil, ciprofibrate, niacin (nicotinic acid), erythromycin, cyclosporin)	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): 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. Since an increased risk of myopathy and/or rhabdomyolysis has been observed in patients receiving HMGCoA reductase inhibitors together with any of these molecules, the benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution 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. 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 in which Lescol XL tablets (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 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 maintenance	Not applicable

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	dose of fluvastatin should be as low as possible when combined with ciclosporin.	
Missing information		
Use in paediatric patients < 9 years of age	SmPC Section 4.4 (Special warnings and precautions for use): Fluvastatin has only been investigated in children of 9 years and older with heterozygous familial hypercholesterolaemia. 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.	Not applicable.
Use during lactation	Based on preclinical data, it is expected that fluvastatin is excreted into human milk. There is insufficient information on the effects of fluvastatin in newborns / infants.	Not applicable.

13.2 Part VI.2 Elements for a Public Summary

13.2.1 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.

13.2.2 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.

13.2.3 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).

13.2.4 Part VI.2.4 Summary of safety concerns

Table 13-5 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*	Some evidence suggests that the	Yes, by monitoring patients at

Risk	What is known	Preventability
onset diabetes mellitus)	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.	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.
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 13-6 Important potential risks

Risk	What is known
Use during pregnancy	There is insufficient data on the use of fluvastatin during pregnancy.

Risk	What is known
	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 13-7 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.

13.3 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.

13.4 Part VI.2.6 Planned post authorization development plan

Not applicable.

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

Not applicable.

14 Part VII Risk Management Plan Annexes

Annex 1 Eudravigilance Interface

Available in electronic format only.

Annex 2 SmPC and Package Leaflet

Current approved SmPC and Package leaflet

The current approved EU MRP Product Information [Summary of Product Characteristics and Package Leaflet] for Lescol/ Lescol XL are presented in Module 1.3.5 of the dossier.

Proposed SmPC and Package leaflet

The Proposed EU MRP Product Information [Summary of Product Characteristics and Package Leaflet] for Lescol/ Lescol XL are presented in Module 1.3.1 of the dossier.

Annex 3 Worldwide marketing authorization by country (including EEA)

Data presented in the following tables are provided from Lescol/ Lescol XL PSUR 17, DLP 31-Aug-2012 and its addendum report. For each Lescol/ Lescol XL presentation, data are displayed by formulation, dosage and country.

Table 14-1 Novartis worldwide Marketing Authorization status for Lescol 20 mg Capsules

Country	Approval Date	Launch date	Trade name (when different from Product)
United Kingdom	23-Aug-1993	31-Jan-1994	-
Canada	21-Dec-1993	30-Mar-1994	-
Switzerland	30-Dec-1993	12-Sep-1994	Lescol Mite
United States of America	31-Dec-1993	23-Mar-1994	-
Malta	01-Feb-1994	15-Feb-1995	-
Egypt	03-Feb-1994	14-Jun-1994	Deregistered
New Zealand	17-Mar-1994	01-Dec-1996	-
Brazil	02-May-1994	10-Apr-1995	De-registered on 02-May-2009
Pakistan	19-May-1994	21-Aug-1995	-
Germany	29-Jun-1994	01-Sep-1994	Locol Also marketed as Cranoc (Novartis Pharma GmbH)
Russia	29-Jun-1994	15-Sep-1994	-
Honduras	01-Jul-1994	01-Mar-1995	-
Hong Kong	01-Jul-1994	01-Mar-1995	Lochol
Curacao	15-Jul-1994	01-Dec-1994	-
Aruba	18-Jul-1994	01-Dec-1994	-
Mexico	11-Aug-1994	01-Dec-1994	-
Guatemala	07-Sep-1994	-	-
Australia	19-Sep-1994	01-Feb-1996	Also marketed as Vastin
Czech Republic	19-Oct-1994	02-Jan-1995	Deregistered on 31-Dec-2010
El Salvador	26-Oct-1994	01-Dec-1994	-
Philippines	27-Oct-1994	31-Mar-1995	-
Trinidad & Tobago	01-Nov-1994	01-Jan-1995	-
Cyprus	10-Nov-1994	15-Nov-1994	-
Jamaica	13-Jan-1995	01-Feb-1995	-
South Africa	13-Jan-1995	20-Feb-1995	-
Nicaragua	13-Feb-1995	01-Dec-1994	-
Panama	16-Feb-1995	03-Apr-1995	-
Argentina	28-Feb-1995	01-Sep-1995	Lochol
Kuwait	14-Mar-1995	01-Apr-1995	-
Slovakia	15-Mar-1995	30-Oct-1995	-
Indonesia	05-Apr-1995	01-Jul-1995	-
Italy	10-Apr-1995	04-Sep-1995	Also marketed as Primesin (Novartis Farma S.p.A) & Lipaxan (Novartis Farma S.p.A.)

Country	Approval Date	Launch date	Trade name (when different from Product)
Sweden	24-May-1995	21-Aug-1995	-
Poland	29-May-1995	25-Aug-1995	-
The Netherlands	12-Jun-1995	09-Oct-1995	-
Austria	26-Jun-1995	Oct-1995	-
Chile	03-Jul-1995	-	Deregistered on 02-Dec-2011
Ecuador	06-Jul-1995	-	Deregistered
Luxembourg	19-Jul-1995	01-Sep-1995	Locol
Denmark	07-Aug-1995	20-Nov-1995	-
Jordan	20-Aug-1995	04-Nov-1996	-
Iraq	22-Aug-1995	-	-
France	04-Sep-1995	31-Jul-1996	Also marketed as Fractal (Pierre Fabre medicament)
Ireland	19-Sep-1995	31-May-1996	-
Israel	15-Oct-1995	25-Feb-1996	-
Nigeria	15-Oct-1995	15-Oct-1995	-
Thailand	24-Oct-1995	01-Feb-1996	-
Singapore	31-Oct-1995	18-Mar-1996	-
Ghana	15-Nov-1995	-	-
Finland	20-Nov-1995	01-Apr-1996	-
Greece	28-Nov-1995	-	-
United Arab Emirates	11-Dec-1995	04-Jan-1996	-
Korea (South)	15-Feb-1996	15-Aug-1996	Also marketed as Xilep (Sandoz Korea)
Spain	21-Feb-1996	-	Also Marketed as Lymetel (Lab. Andromaco), Digaril (Novartis Farmaceutica S.A.), Vaditon (Laboratorios Visfarm S.L.), Liposit (Novartis Farmaceutica S.A.)
Kenya	13-Mar-1996	15-Aug-1995	-
Portugal	30-Mar-1996	01-Sep-1997	Also marketed as Cardiol (Bialport), Canef (Laboratorio Normal - Produtos Farmaceuticos, S.A.)
Saudi Arabia	04-Apr-1996	31-Jul-1997	-
Sudan	06-Apr-1996	-	-
Belgium	09-Apr-1996	-	-
Taiwan	10-May-1996	-	-
Bahrain	18-Sep-1996	-	-
Malaysia	21-Nov-1996	22-Apr-1997	-
Norway	25-Nov-1996	01-Jan-1997	-
Qatar	21-Dec-1996	-	-
Uganda	23-Jan-1997	-	-
Romania	15-May-1997	-	-
China	31-May-1997	31-Aug-1997	-
Iceland	03-Sep-1997	01-Oct-1997	-
Serbia & Montenegro	03-Dec-1997	31-Dec-1997	-

Country	Approval Date	Launch date	Trade name (when different from Product)
Oman	10-Jun-1998	-	-
Bangladesh	03-Aug-1998	02-May-2000	-
Tanzania	18-Oct-2000	-	-
Macedonia	28-Jun-2001	21-Jun-2006	Deregistered on 18-Jun-2011
Namibia	18-Aug-2004	-	-
Yemen	25-Oct-2005	-	-
Tunisia	16-Jan-2006	-	-

Table 14-2 Novartis worldwide Marketing Authorization status for Lescol 40 mg Capsules

Country	Approval Date	Launch date	Trade name (when different from Product)
United Kingdom	23-Aug-1993	31-Jan-1994	-
Cameroon	20-Dec-1993	02-Aug-2006	-
Canada	21-Dec-1993	30-Mar-1994	-
Switzerland	30-Dec-1993	12-Sep-1994	Lescol Mite
United States of America	31-Dec-1993	23-Mar-1994	-
Hungary	31-Jan-1994	15-Oct-1994	-
Malta	01-Feb-1994	15-Feb-1995	-
Egypt	22-Feb-1994	14-Jun-1994	Deregistered on 05-May-2010
New Zealand	17-Mar-1994	01-Dec-1996	-
Brazil	02-May-1994	10-Apr-1995	Deregistered on 26-Oct-2010
Pakistan	19-May-1994	15-Jan-1999	-
Germany	29-Jun-1994	01-Sep-1994	Locol Also marketed as Cranoc (Novartis Pharma GmbH),
Russia	29-Jun-1994	15-Sep-1994	-
Hong Kong	01-Jul-1994	01-Mar-1995	Lochol
Curacao	15-Jul-1994	01-Dec-1994	-
Aruba	18-Jul-1994	15-Jan-1995	-
Mexico	11-Aug-1994	01-Dec-1994	-
Guatemala	07-Sep-1994	01-Dec-1994	-
Australia	19-Sep-1994	01-Feb-1996	Also marketed as Vastin
Czech Republic	19-Oct-1994	-	Deregistered on 31-Dec-2010
El Salvador	26-Oct-1994	01-Dec-1994	-
Philippines	27-Oct-1994	31-Mar-1995	Lochol
Trinidad & Tobago	01-Nov-1994	01-Jan-1995	-
Cyprus	10-Nov-1994	15-Nov-1994	-
Honduras	18-Nov-1994	01-Dec-1994	-
Nigeria	12-Dec-1994	15-Oct-1995	-
Jamaica	13-Jan-1995	01-Feb-1995	-
South Africa	13-Jan-1995	20-Feb-1995	-
Nicaragua	13-Feb-1995	01-Dec-1994	-
Panama	16-Feb-1995	03-Apr-1995	-
Argentina	28-Feb-1995	01-Sep-1995	-
Kuwait	14-Mar-1995	01-Apr-1995	-

Country	Approval Date	Launch date	Trade name (when different from Product)
Slovakia	15-Mar-1995	30-Oct-1995	-
Indonesia	05-Apr-1995	01-Jul-1995	-
Italy	10-Apr-1995	04-Sep-1995	Also marketed as Primesin (Novartis Farma S.p.A.) & Lipaxan (Novartis Farma S.p.A.).
Bulgaria	25-Apr-1995	-	-
Sweden	24-May-1995	21-Aug-1995	-
Poland	29-May-1995	25-Aug-1995	-
The Netherlands	12-Jun-1995	09-Oct-1995	-
Austria	26-Jun-1995	01-Oct-1995	Lescol
Chile	03-Jul-1995	-	Deregistered on 02-Dec-2011
Ecuador	06-Jul-1995	15-Sep-1995	Deregistered
Luxembourg	19-Jul-1995	01-Sep-1995	Locol
Denmark	07-Aug-1995	20-Nov-1995	-
Jordan	20-Aug-1995	04-Nov-1996	-
Iraq	22-Aug-1995	-	-
France	04-Sep-1995	31-Jul-1996	Also Marketed as Fractal (Pierre Fabre Medicament)
Croatia	15-Sep-1995	15-May-1996	-
Ireland	19-Sep-1995	31-May-1996	-
Korea	22-Sep-1995	-	Also marketed as Xilep (Sandoz Korea)
Estonia	04-Oct-1995	15-Feb-1996	Deregistered on 11-Nov-2010
Yemen	10-Oct-1995	-	-
Israel	15-Oct-1995	25-Feb-1996	-
Thailand	24-Oct-1995	01-Feb-1996	-
Singapore	31-Oct-1995	18-Mar-1996	-
Finland	20-Nov-1995	01-Apr-1996	-
Greece	28-Nov-1995	02-Sep-1996	-
Palestine	11-Dec-1995	02-Aug-2006	-
Turkey	12-Dec-1995	09-Mar-1996	-
United Arab Emirates	12-Dec-1995	04-Jan-1996	-
Spain	21-Feb-1996	-	Also marketed as Lymetel (Lab. Andromaco), Digaril (Novartis Farmaceutica S.A.), Vaditon (Laboratorios Visfarm S.L.), Liposit (Novartis Farmaceutica S.A.)
Kenya	13-Mar-1996	15-Aug-1995	-
Portugal	30-Mar-1996	01-Sep-1997	Also marketed as Cardiol (Bialport), Canef (Laboratorio Normal - Produtos Farmacêuticos S.A.)
Saudi Arabia	04-Apr-1996	31-Jul-1997	Deregistered on 09-Aug-2010
Sudan	06-Apr-1996	02-Aug-2006	-
Belgium	09-Apr-1996	01-May-1997	-
Bahrain	18-Sep-1996	-	-
Ivory Coast	17-Oct-1996	02-Aug-2006	-
Malaysia	21-Nov-1996	22-Apr-1997	-

Country	Approval Date	Launch date	Trade name (when different from Product)
Norway	25-Nov-1996	01-Jan-1997	-
Burkina Faso	29-Nov-1996	-	-
Qatar	21-Dec-1996	-	-
Taiwan	10-Jan-1997	-	-
Lebanon	11-Feb-1997	30-Jul-1997	-
Madagascar	14-Feb-1997	02-Aug-2006	-
Romania	15-May-1997	-	-
China	31-May-1997	31-Aug-1997	-
Mali	31-May-1997	-	-
Mauritius	14-Aug-1997	02-Aug-2006	-
Iceland	03-Sep-1997	01-Oct-1997	-
Slovenia	11-Nov-1997	30-Dec-1997	-
Serbia & Montenegro	03-Dec-1997	31-Dec-1997	-
Senegal	20-Mar-1998	02-Aug-2006	-
Oman	10-Jun-1998	-	-
Bangladesh	03-Aug-1998	02-May-2000	-
Albania	20-Jan-2000	-	-
Bosnia Herzegovina	12-Apr-2000	-	Deregistered on 22-Jun-2012
Algeria	06-Jun-2000	02-Aug-2006	
Macedonia	28-Jun-2001	21-Jun-2006	Deregistered on 18-Jun-2011
Haiti	28-Nov-2001	Deregistered on 04-Nov-2009	-
Gabon	26-Apr-2002	02-Aug-2006	-
Syria	18-May-2002	02-Aug-2006	-
Congo (Brazzaville)	18-Jul-2003	02-Aug-2006	-
Guinea	31-Dec-2003	02-Aug-2006	-
Namibia	18-Aug-2004	-	-
Tunisia	16-Jan-2006	-	-
Ghana	23-May-2006	21-Aug-2006	-
Congo, Democratic Republic	20-Jul-2006	02-Aug-2006	-
Togo	02-Aug-2006	-	-

Table 14-3 Novartis worldwide Marketing Authorization status for Lescol 10 mg, 20 mg, 30 mg Tablets

Country	Approval Date	Launch date	Trade name (when different from Product)
Japan	06-Feb-2003	26-Jun-2003	Lochol Tablets 10mg (Tanabe)
Japan	06-Feb-2003	26-Jun-2003	Lochol Tablets 20 mg (Tanabe)
Japan	06-Feb-2003	26-Jun-2003	Lochol Tablets 30mg (Tanabe)

Table 14-4 Novartis worldwide Marketing Authorization status for Lescol XL 80 mg Prolonged Release Tablets

Country	Approval Date	Launch date	Trade name (when different from Product)
Brazil	25-Jul-2000	28-Feb-2001	-
Portugal	28-Jul-2000	Nov 2001	Also marketed as Cardiol (Bialport), Canef

Country	Approval Date	Launch date	Trade name (when different from Product)
			(Laboratorio Normal - Produtos Farmacêuticos, S.A.)
Austria	09-Aug-2000	01-Apr-2001	Lescol MR
United Kingdom	10-Aug-2000	30-Sep-2000	-
Switzerland	29-Aug-2000	01-Dec-2000	Lescol Forte
Argentina	21-Sep-2000	30-Sep-2001	Lescol LC
Latvia	27-Sep-2000	03-Oct-2000	-
United States of America	06-Oct-2000	31-Dec-2000	-
Malta	10-Oct-2000	01-Mar-2001	-
Denmark	13-Oct-2000	06-Jan-2003	Lescol Depot
Thailand	16-Oct-2000	02-Nov-2000	-
New Zealand	02-Nov-2000	-	-
Mexico	09-Nov-2000	-	-
Ecuador	29-Nov-2000	-	-
Cyprus	12-Dec-2000	30-Dec-2000	-
Estonia	21-Dec-2000	01-Aug-2001	-
Peru	29-Dec-2000	02-May-2001	Deregistered on 07-Apr-2009
Mauritius	19-Jan-2001	-	-
Israel	01-Feb-2001	28-Jul-2002	Deregistered on 22-Apr-2010
Chile	09-Feb-2001	-	Deregistered on 02-Dec-2011
Bahrain	11-Feb-2001	31-Mar-2001	-
Kuwait	24-Feb-2001	30-Sep-2001	-
France	27-Feb-2001	Sep-2001	Lescol-LP Also marketed as Fractal (Pierre Fabre Medicament)
Vietnam	19-Mar-2001	-	-
Czech Republic	21-Mar-2001	01-Jul-2001	-
Germany	27-Mar-2001	17-Apr-2001	Locol Also marketed as Cranoc (Novartis Pharma GmbH)
Palestine	16-Apr-2001	01-Aug-2001	-
Korea	20-Apr-2001	01-Aug-2001	Also marketed as Xilep XL (Sandoz Korea)
Singapore	26-Apr-2001	24-Aug-2001	-
Bulgaria	02-May-2001	-	-
Slovakia	04-May-2001	30-Sep-2002	-
Egypt	28-May-2001	06-Jun-2001	-
United Arab Emirates	11-Jun-2001	30-Jun-2002	-
Lithuania	15-Jun-2001	-	-
The Netherlands	19-Jun-2001	29-Aug-2001	-
Philippines	29-Jun-2001	18-Jul-2001	-
Sweden	29-Jun-2001	02-Sep-2002	Lescol Depot
Sri Lanka	04-Jul-2001	-	Deregistered
Colombia	05-Jul-2001	30-Apr-2002	
Italy	09-Jul-2001	06-Nov-2001	Also marketed as Primesin (Novartis Farma S.p.A.) & Lipaxan (Novartis Farma S.p.A.)
Poland	26-Jul-2001	22-Oct-2001	-

Country	Approval Date	Launch date	Trade name (when different from Product)
Qatar	30-Jul-2001	31-Mar-2002	-
Hong Kong	19-Sep-2001	-	-
Madagascar	03-Oct-2001	-	-
Russia	08-Oct-2001	30-Dec-2003	Lescol Forte
Finland	17-Dec-2001	28-Jan-2002	Lescol Depot
Hungary	19-Dec-2001	01-Apr-2002	-
Luxembourg	21-Dec-2001	-	Locol
Norway	21-Dec-2001	15-Jul-2002	Lescol Depot
Oman	25-Dec-2001	31-Jan-2002	-
Kenya	31-Dec-2001	-	-
Belgium	07-Jan-2002	01-Sep-2002	Lescol-exel 80
Ireland	23-Jan-2002	02-Aug-2006	-
Yemen	04-Feb-2002	31-May-2002	-
Spain	18-Mar-2002	-	Also marketed as Lymetel (Lab.- Andromaco), Digaril Prolib (Novartis Farmaceutica S.A.), Vaditon Prolib (Laboratorios Visfarm S.L.), Liposit Prolib (Novartis Farmaceutica S.A.)
Saudi Arabia	19-Mar-2002	31-Mar-2002	-
Jordan	25-Apr-2002	02-Aug-2006	-
South Africa	20-May-2002	-	-
Albania	23-Jul-2002	-	-
Iraq	14-Aug-2002	-	-
Australia	17-Sep-2002	02-Aug-2007	-
Indonesia	30-Sep-2002	01-Oct-2004	-
Taiwan	02-Oct-2002		-
Lebanon	07-Nov-2002	02-Aug-2006	-
Greece	16-Dec-2002	31-Jan-2004	-
Serbia & Montenegro	28-Dec-2002	28-Dec-2002	-
Romania	31-Dec-2002	01-Oct-2003	-
Turkey	26-Feb-2003	03-Mar-2003	-
Malaysia	21-Mar-2003	30-Jun-2003	-
Morocco	02-Jul-2003	-	Lescol LP
Iceland	22-Sep-2003	01-Jun-2004	Lescol Depot
India	25-Nov-2003	-	-
Slovenia	27-Jan-2004	11-May-2004	-
Canada	22-Mar-2004	18-Jun-2004	Lescol XL
Bangladesh	31-Jul-2004	01-Oct-2004	-
Namibia	18-Aug-2004	-	-
Guinea	24-Aug-2004	-	-
Pakistan	26-Aug-2004	15-Dec-2004	-
Croatia	28-Sep-2004	24-Feb-2005	-
Cuba	18-Apr-2005	-	Deregistered on 18-Mar-2010
Mali	12-Sep-2005	-	-
Macedonia	28-Sep-2005	-	-
Nigeria	29-Nov-2005	10-May-2006	-
Zambia	28-Feb-2006	-	-

Country	Approval Date	Launch date	Trade name (when different from Product)
Ghana	23-May-2006	20-Nov-2006	-
Uzbekistan	14-Jul-2006	-	-
Tanzania	02-Aug-2006	-	-
Botswana	01-Mar-2007	-	-
Algeria	07-Mar-2007	-	-
Belarus	30-Mar-2007	-	-
Ukraine	06-Aug-2007	15-Jan-2008	-
Bosnia-Herzegovina	12-Sep-2007	12-Sep-2007	
Republic Srpska	19-Oct-2007	-	Deregistered on 15-Dec-2009
Togo	30-Jan-2008	-	-
Azerbaijan	27-Feb-2008	-	-
Armenia	23-Jun-2008	-	-
Moldova	04-Jul-2008	-	-
Cambodia	29-Jul-2008	-	-
China	09-Apr-2009	15-Oct-2009	-
Tunisia	03-Jun-2009	04-Jan-2010	Lescol LP
Sudan	08-Oct-2009	-	-
Senegal	31-Jan-2011	-	-
Ivory Coast	21-Feb-2011	-	-
Kosovo	20-Mar-2012	-	-

Table 14-5 Sandoz worldwide Marketing Authorization status for Lescol 20 mg Capsules

Country	Trade Name	MA Number	MA Date	Launch Date	MAH
Austria	Fluvastatin Sandoz 20 mg -Hartkapseln	1-27223	15-Oct-2007	-	Sandoz GMBH
Belgium	Fluvastatin Sandoz 20 mg harde capsules	1472 IS 426 F4 1472 IS 427 F4	08-Oct-2007	-	Sandoz N.V.
Denmark	Fluvastatin sandoz	39846	16-Oct-2007	-	Sandoz A/S
Denmark	Fluvastaham	39848	06-Oct-2007	-	Sandoz A/S
Denmark	Fluvastadig	39850	16-Oct-2007	-	Sandoz A/S
France	Fluvastatine sandoz 20 mg, Gélule	3400957205614 3400938350012 3400938349931 3400938349870 3400938349702 3400938349641 3400938349580 3400938349412 3400938349351 3400938349290 3400938349122 3400938349061	23-Jan-2008	25-Aug-2008	Sandoz S.A.S.
Germany	Fluvastatin sandoz 20 mg Hartkapseln	66372.00.00	14-Jan-2008	25-Aug-2008	Sandoz Pharmaceuticals GMBH
Germany	Fluvastatin hexal 20 mg Hartkapseln	66400.00.00	14-Jan-2008	20-Aug-2008	Hexal AG
Germany	Fluvastatin - 1a	66398.00.00	14-Jan-2008	01-Sep-2008	1 A Pharma

Country	Trade Name	MA Number	MA Date	Launch Date	MAH
	pharma 20mg hartkapseln				GMBH
Ireland	Fluvat 20 mg capsules pa	711/117/1	25-Jan-2008	-	Rowex LTD
Italy	Fluvastatina sandoz	03354201	01-Aug-2000	29-Jun-2009	Sandoz S.P.A.
Luxembourg	Fluvastatin hexal 20 mg Kapseln	04800650480079 0480082 0480096 0480101 0480115 0480129 0480132 0480146 0480163 0480177 0480181 0715/08040029	21-Apr-2008	-	Hexal AG
Netherlands	Fluvastatine sandoz 20 mg rvg	34405	28-Jan-2008	25-Aug-2008	Sandoz B.V.
Portugal	Fluvastatina sandoz	5090279 5090303 5090311	27-Feb-2008	07-May-2009	Sandoz Farmacéutica LDA
Spain	Fluvastatina sandoz 20 mg Cápsulas efg	69885	14-May-2008	01-Jan-2003	Sandoz Farmacéutica S.A.
Spain	Fluvastatina bexal 20 mg Cápsulas efg	69856	09-Jun-2008	05-Dec-2008	Bexal Farmaceutica S.A.
Spain	Fluvastatina acost 20 mg Cápsulas efg	70325	16-Dec-2008	-	Bexal Farmaceutica S.A.
Switzerland	Fluvastatin sandoz mite	58491	24-Sep-2008	-	Sandoz Pharmaceuticals AG
United Kingdom	Fluvastatin 20 mg capsules	PL 04416/0748	30-Nov-2007	27-Aug-2008	Sandoz LTD.

Table 14-6 Sandoz worldwide Marketing Authorization status for Lescol 40 mg Capsules

Country	Trade Name	MA Number	MA Date	Launch Date	MAH
Albania	Fluvastatin - 1 A Pharma 40 mg Hartkapseln	6315	12-Oct-2011	-	1A Pharma GmBH
Austria	Fluvastatin Sandoz 40 mg - Hartkapseln	1-27224	15-Oct-2007	-	Sandoz GmBH
Belgium	Fluvastatin Sandoz 40 mg harde capsules	1472 IS 428 F4 1472 IS 429 F4	08-Oct-2007	26-Apr2012	Sandoz N.V.
Denmark	Fluvastatin Sandoz	39847	16-Oct-2007	-	Sandoz A/S
Denmark	Fluvastaha	M 39849	16-Oct-2007	-	Sandoz A/S
Denmark	Fluvastadi G	39851	16-Oct-2007	-	Sandoz A/S
France	Fluvastatine Sandoz 40 Mg, Gélule	3400957205843 3400938352542 3400938352313	23-Jan-2008	25-Aug-2008	Sandoz S.A.S.

Country	Trade Name	MA Number	MA Date	Launch Date	MAH
		3400938352252 3400938352191 3400938352023 3400938351941 3400938351880 3400938351712 3400938351651 3400938351590 3400938351422			
Germany	Fluvastatin sandoz 40 mg Hartkapseln	66373.00.00	14-Jan-2008	25-Aug-2008	Sandoz pharmaceuticals Gmbh
Germany	Fluvastatin hexal 40 mg Hartkapseln	66401.00.00	14-Jan-2008	25-Aug-2008	Hexal AG
Germany	Fluvastatin - 1a pharma 40 Mg hartkapslen	66399.00.00	14-Jan-2008	01-Sep-2008	1A pharma gmbh
Ireland	Fluvat 40 mg capsules	PA 711/117/2	25-Jan-2008	-	Rowex Ltd
Italy	Fluvastatina sandoz	033542022 033542034	Aug/1/2000	-	Sandoz s.p.a.
Luxembourg	Fluvastatin hexal 40 mg Kapseln	0715/08040030 0480311 0480308 0480292 0480289 0480275 0480261 0480258 0480244 0480231 0480227 0480213 0480194	Apr/21/2008	-	Hexal AG
Netherlands	Fluvastatine sandoz 40 mg rvg	34406	Jan/28/2008	25-Aug-2008	Sandoz B.V.
Portugal	Fluvastatina sandoz	5090329 5090337 5090345	Feb/27/2008	07-May-2009	Sandoz Farmacéutica LDA
Spain	Fluvastatina sandoz 40 mg Cápsulas efg	69886	May/14/2008	01-Jan-2003	Sandoz Farmacéutica S.A.
Spain	Fluvastatina bexal 40 mg Cápsulas efg	69857	Jun/9/2008	05-Dec-2008	Bexal Farmaceutica S.A.
Spain	Fluvastatina acost 40 mg Cápsulas efg	70328	16-Dec-2008	-	Bexal Farmaceutica S.A.
Switzerland	Fluvastatin Sandoz	58491	24-Sep-2008	01-Oct-2008	Sandoz Pharmaceuticals AG
United Kingdom	Fluvastatin 40 mg capsules	PL04416/0749	30-Nov-2007	27-Aug-2008.	Sandoz LTD

Table 14-7 Sandoz worldwide Marketing Authorization status for Lescol XL 80 mg Prolonged Release Tablets

Country	Trade Name	MA Number	MA Date	Launch Date	MAH
Austria	Fluvastatin Sandoz 80 mg -Retardtabletten	1-28044	25-Feb-2009	-	Sandoz GMBH
Belgium	Fluvastatin Sandoz 80 mg tabletten met verlengde afgifte	BE332701 BE332717 BE332726	24-Jun-2011	26-Apr-2012	Sandoz N.V.
Croatia	Fluvascol	UP/I-530-09/08-01/19 UP/I-530-09/08-01/20	13-Nov-2008	01-Jun-2012	Sandoz D.O.O.
Denmark	Fluvastasof	40367	28-Apr-2008	-	Sandoz A/S
Denmark	Fluvastamil	40366	28-Apr-2008	-	Sandoz A/S
Denmark	Vuyator 80 mg	41032	18-Sep-2008	-	Sandoz A/S
Finland	Fluvastatin sandoz 80 mg depottabletti	22944	21-Jul-2008	25-Oct-2011	Sandoz A/S
France	Fluvastatine Sandoz LP 80Mg, comprimé pelliculé à Libération prolongée	573 102-7 573 101-0 573 100-4 387 975-4 387 973-1 387 972-5 386 720-2 386 719-4 386 718-8 386 717-1 386 716-5 386 715-9	19-Aug-2008	10-Feb-2012	Sandoz S.A.S.
Germany	Fluvastatin Hexal® 80 mg Retardtabletten	67843.00.00	05-Aug-2008	01-Oct-2008	Hexal AG
Germany	Fluvastatin - 1a pharma 80mg retardtabletten	67869.00.00	05-Aug-2008	01-Sep-2008	1A Pharma GmBH
Hungary	Fluvastatin sandoz 80 mg retard Tabletta	OGYI-T-20650/01 OGYI-T-20650/02 OGYI-T-20650/03 OGYI-T-20650/04	20-Oct-2008	20-Jul-2009	Sandoz Hungaria KFT
Ireland	Fluvat 80 mg prolongedrelease Tablets	PA 711/117/3	30-Apr-2009	-	Rowex LTD
Italy	Fluvastatina sandoz gmbh 80 mg compresse a rilascio Prolungato	038579102/M 038579090/M 038579088/M 038579076/M 038579064/M 038579052/M 038579049/M 038579037/M 038579025/M 038579013/M	17-Mar-2009	21-Dec-2009	Sandoz GmBH
Italy	Fluvastatina sandoz	033542046	01-Aug-2000	-	Sandoz S.P.A.
Luxembourg	Fluvastatin Hexal® 80 mg Retardtabletten	0715/08120036 0498981 0498977 0498963 0498946	23-Dec-2008	-	Hexal AG

Country	Trade Name	MA Number	MA Date	Launch Date	MAH
		0498932 0498929 0498915 0498901 0498896 0498882 0498879 0498865			
Netherlands	Fluvastatine sandoz Retard 80 mg, tabletten Met verlengde afgifte Rvg	35264	23-Mar-2009	01-May-2009	Sandoz B.V.
Portugal	Fluvastatina sandoz	5113816 5113824 5113832	30-May-2008	01-May-2009	Sandoz farmacéutica lda
Slovakia	Vuyator 80 mg tablety s predĺženým Uvoľňovaním	31/0359/08-S	12-Nov-2008	01-Jan-2010	Sandoz pharmaceuticals d.d.
Spain	Fluvastatina prolib bexal 80 mg comprimidos de Liberación prolongada efg	70282	20-Nov-2008	-	Bexal farmaceutica s.a.
Spain	Fluvastatina prolib acost 80 mg comprimidos de Liberación prolongada efg	70028	14-Aug-2008	04-Nov-2009	Sandoz farmacéutica s.a.
Switzerland	Fluvascol sandoz retard	58515	22-Sep-2009	-	Sandoz Pharmaceuticals AG
Switzerland	Fluvastatin Sandoz Retard	59364	12-Mar-2009	-	Sandoz pharmaceuticals AG

Annex 4 Synopsis of ongoing and completed clinical trial program

Please refer Table 14-8 below.

Table 14-8 List ongoing and completed clinical trial program

Study	Description (Phase, short description of study (1 – 2 sentences including comparator names/placebo))	Countries	Study design	Planned/actual t. n. of patients	Duration of follow up	Estimated/Actual completion date
Placebo controlled (PB)						
6 (Novartis, formerly Sandoz Pharmaceuticals)	Evaluation of Safety and Efficacy of XU 62·320 Administered Orally to Patients with Elevated LDL-C Utilizing a BID or QAM Dosing Regimen	US	RAND, DB, PBO FL 7.5 mg BID 15 mg QAM PBO	Planned: 36/ 25 8 8 9	4 wk	First patient entered: December 1987 last patient completed: July 1988
7 (Novartis, formerly Sandoz Pharmaceuticals)	Evaluation of Safety and Efficacy of XU 62-320 Administered Orally to Patients with Elevated LDL·C Utilizing a QAM or QPM Dosing Regimen	US	RAND, DB, PBO, PG 15 mg QAM 15 mg QPM PBO	Planned: 36/ 33 11 11 11	4 wk	First patient entered: December 1987 Last patient completed: September 1988
8 (Novartis, formerly Sandoz Pharmaceuticals)	Outpatient Double-Blind Evaluation of Safety and Efficacy of XU 62-320 Administered Orally to Patients with Elevated LDL·C Utilizing a QAH or QPH Dosing Regimen	US	RAND, DB, PBO, PG FL 5 mg TID 7.5 mg BID 15 mg QPM PBO	Planned: 64/ 82 20 21 21 20	4 wk	first patient entered: October 1987 last patient completed: April1988
12 (Novartis, formerly Sandoz Pharmaceuticals)	Multicenter, Outpatient, Double-Blind Evaluation of the Safety and Efficacy of Fluvastatin (XU 62-320) Administration in a QPM Dosing Regimen at 5, 15, 30 and 40 mg (A Dose Response Study) (Doc #603-164)	US	RAND, DB, PBO, PG FL 5 mg QPM 15 mg QPM 30 mg QPM 40 mg QPM PBO	Planned unk./ 424 85 83 82 88 86	6 wk	9/88
13 (Novartis, formerly Sandoz	Multicenter Outpatient Double-Blind Evaluation of the Safety and Efficacy of Fluvastatin (XU 62-320) Administered as 10 mg BID or 20 mg QPM (A Dose Frequency Study) (Doc #603·165)	US	RAND,DB,PBO, PG FL 10 mg BID 20 mg QPM	Planned unk./ 207 69	6 wk	(8/88)

Study	Description (Phase, short description of study (1 – 2 sentences including comparator names/placebo))	Countries	Study design	Planned/actual t. n. of patients	Duration of follow up	Estimated/Actual completion date
Pharmaceuticals)			PBO	70 68		
20 (Novartis, formerly Sandoz Pharmaceuticals)	Multicenter Double-Blind Evaluation of the Safety and Efficacy of Fluvastatin (XU 62-320)	US	RAND, DB, PBO, PG	Planned unk./ 602	27 wk	(9/89)
			FL 20 mg OPM 20-40 mg QPM	217 82		
			PBO	303		
20Ext (Novartis, formerly Sandoz Pharmaceuticals)	Multicenter· Double-Blind Evaluation of the Safety and Efficacy of Fluvastatin (XU 62-320) with the PRN Addition of Cholestyramine (CME) in Patients with Inadequate Response to Fluvastatin Alone	US	Rand, DB, PBO, PG	Planned 400/ 542	54 wk (total)	first patient entered: September 1989 last patient completed: August 1991
			FL 20 mg, 40 mg QPM	205		
			20 mg, 40 mg QPM + 16 g CME	69		
			PBO PBO + CME	97 171		
22 (Novartis, formerly Sandoz Pharmaceuticals)	Multicenter Double-Blind Evaluation of the Safety and Contribution to the Efficacy of Concomitant Fluvastatin (XU 62-320) and Open-Label Cholestyramine	US	RAND, DB, PBO, PG	Planned 240/ 224	24 wk	first patient entered; 26th January 1990 last patient completed: 4th February 1991
			FL 10 mg QPM 20 mg QPM 10 mg QPM + 8-16 g CME	39 38 36		
			20 mg QPM + 8-16 g CME	37 37		

Study	Description (Phase, short description of study (1 – 2 sentences including comparator names/placebo))	Countries	Study design	Planned/actual t. n. of patients	Duration of follow up	Estimated/Actual completion date
			PBO	37		
			PBO + 8-16 g CME			
26 (Novartis, formerly Sandoz Pharmaceuticals)	Multicenter Double-Blind Evaluation of the Safety and Efficacy of Fluvastatin (XU 62-320) Administration at 20 mg QPM, 40 mg QPM, or 20 mg BID in High Risk Patients	US	RAND, DB, PBO, PG	430	12 wk	4/90
			FL 20 mg QPM	108		
			20 mg BID	107		
			40 mg QPM	107		
			PBO	108		
26A5 (Novartis, formerly Sandoz Pharmaceuticals)	Three-Month Extension of the Evaluation of the Safety and ·Efficacy of Fluvastatin (XU 62-320) Administration at 20 mg QPM, 40 mg QPM, or 20 mg BID in High Risk Patients	US	RAND, DB, PBO, PG	396	24 wk total	first patient entered: September 1990
			Fl 20 mg QPM	100		last patient completed: May 1991
			20 mg BID	99		
			40 mg QPH	97		
			PBO (6 weeks only)	100		
XUO-F253-E-00 (Sandoz)	Determine lipid lowering effect of fluvastatin MR 160 mg administered as two 80 mg tablets compared to fluvastatin MR 80mg and 40 mg Lescol IR	USA	RAND, DB,	123	6 wk	FPFV: 16 Mar 98 LPLV: 27 Nov 98
			Fluv. MR 160	40		
			Fluv. MR 80	42		
			Lescol 40	41		
XUO-F302-E-00 (Novartis, formerly Sandoz Pharmaceuticals)	Demonstrate superiority lipid lowering effect of fluvastatin MR 80 my QPM compared to Lescol IR 40 mg OPM In Hypercholesterolemic type IIa and IIb patients	Switzerland, Czech Republic, Germany, Spain, UK, Italy, The Netherlands, Poland	RAND, DB, PG	695	24 wk	FPFV: 16 Apr 98 LPLV: 31 May 99
			Fluvastatin MR 80mg QPM	346		
			Lescol IR 40mg QPM	174		
			Lescol IR 40mg BID	175		

Study	Description (Phase, short description of study (1 – 2 sentences including comparator names/placebo))	Countries	Study design	Planned/actual t. n. of patients	Duration of follow up	Estimated/Actual completion date
		Sweden				
XUO-F351-E-00 (Novartis, formerly Sandoz Pharmaceuticals)	To determine the efficacy of fluvastatin MR 80 mg compared to Lescol IR 40 mg In Hypercholesterolemic type IIa and IIb patients	USA	RAND, DB, PG Fluvastatin MR Lescol IR	555 370 185	24 wk	FPFV: 27 Feb 98 LPLV: 22 Apr 99
CXUO320 EU01 "LIPS" (Serruys et al 2002)	Hypercholesterolemic patients with stable or unstable angina or silent ischemia following successful completion of their first percutaneous coronary intervention.	Belgium, France, Germany, Italy, UK, the Netherlands, Spain, Switzerl., Canada, and Brazil).	RAND, DB Fluv 80 Plac	1677 844 833	208 wk	Oct 1998
XUO-F-353-E-00 (Novartis, formerly Sandoz Pharmaceuticals)	To demonstrate superiority lipid lowering effect of fluvastatin MR 80mg QPM compared to Lescol QR 40mg QPM In Hypercholesterolemic type IIa and IIb patients	USA Canada Australia, South Africa, Turkey	RAND, DB, PG Fluvastatin MR Lescol IR QPM Lescol IR BID	442 141 146 155	24 wk	FPFV: 11 Mar 98 LPLV: 30 Apr 99
XUO-F351-E-01 (Novartis, formerly Sandoz Pharmaceuticals)	Assess long term safety and tolerability and secondarily efficacy of fluvastatin MR Hypercholeslerolemic type lla and IIb patients who have completed XUO-F351-E00	USA	Open-label uncontrolled Fluvastatin MR 80 mg	Planned 450/ 425	28 wk	Nov 1999
CXUO320 F351E2	Extension to CXUO320 F351E1	USA	Open-label uncontrolled	Planned unk/	28 wk	May 2000

Study	Description (Phase, short description of study (1 – 2 sentences including comparator names/placebo))	Countries	Study design	Planned/actual t. n. of patients	Duration of follow up	Estimated/Actual completion date
(Novartis, formerly Sandoz Pharmaceuticals)			Fluvastatin MR 80 mg	207		
	Secondary Prevention		RAND, DB	319	130 wk	Feb 1996
LCAS (Herd et al 1997)	Coronary Atherosclerosis in Patients With Mild to Moderate Cholesterol Elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS])		Fluv 40 Plac	156 163		
21 (Novartis, formerly Sandoz Pharmaceuticals)	Comparator Multicenter, Double-Blind Comparison of the Safety and Efficacy of Fluvastatin (XU 62-320) and Lovastatin	US	RAND, DB, PBO, PG FL 20 mg QPM LOVA 20 mg QPM	349 175 174	24 wk	first patient entered: February 1990 last patient completed: January 1991
98 (Novartis, formerly Sandoz Pharmaceuticals)	Comparator Multicenter, Double-Blind, Long Term Comparison of the Safety and Efficacy Evaluation of Fluvastatin (XU 62-320) and Lovastatin	US	RAND, DB, AC, PG FL 20 mg QPM 20 mg BID LOVA 20 mg QPM 20 mg BID	268 (-4) 134 134		first patient entered: Jan 1991 last patent completed: April1991
Further safety/efficacy studies						
CXUO320 B2406 (Stein et al 2008)	Fluvastatin extended release 80 mg alone or in combination with ezetimibe 10 mg as compared to ezetimibe monotherapy, in dyslipidemic patients with previous history of muscular complaints with other statins.	Germany Norway Russia Turkey USA Greece	RAND, DB flXL 80 mg Ezetimibe alone Comb. of fluvastatin XL 80 mg Ezetimibe	210/ 199 69 66 64	12 wk	Dec 2006
Studies in special populations (e.g. paediatric, elderly)						
CXUO320	Phase IIIb, prospective dose titration study of the	South	OL,	29	2 years	First patient

Study	Description (Phase, short description of study (1 – 2 sentences including comparator names/placebo))	Countries	Study design	Planned/actual t. n. of patients	Duration of follow up	Estimated/Actual completion date
ZA01	efficacy and safety of Lescol (fluvastatin sodium) in the treatment of children with heterozygous familial hypercholesterolemia	Africa				enrolled: 13-Jan-1994 Last patient completed: 31 Aug-1999
CXUO320B 2301	Phase III, Open label, , dose titration, multicenter study to assess the efficacy and safety of fluvastatin sodium capsules and fluvastatin sodium extended release (XL) tablets (20, 40 and 80 mg) given orally at bedtime for 114 weeks in paediatric patients with heterozygous familial hypercholesterolemia	The Netherlands and South Africa	OL	85	2 years	First patient enrolled: 15-Oct-2001 Last patient completed: 07-Mar-2005
Studies in patients with renal impairment						
XUW 303-E-00/001	Phase I, pharmacokinetics of fluvastatin in patients with renal insufficiency following a single oral administration	France	OL, parallel group	Planned: 48 Actual: 48		first subject dosed 09-Mar-93 last subject completed 22-Sep-94
LES-NZ-01	Phase IV, study to investigate the effects of fluvastatin on cardiovascular risk factors in subjects with renal insufficiencyok	New Zealand	RAND, DB, PBO	Planned 40, Actual: 42	12 weeks	First patient enrolled: 24-Jan-1994, Last patient completed: 30-Jun-1994

In addition to the Novartis studies listed here, there are meta-analyses (Naci et al 2013a, Naci et al 2013b) which compared safety and efficacy of various statins and included selected additional study results from publications such as Wright et al 2002 and Anderssen et al 2005.

Annex 5 Synopsis of ongoing and completed pharmaco-epidemiological study program

This annex presents the synopsis of ongoing and completed pharmaco-epidemiological studies which are part of the pharmacovigilance plan.

Ongoing pharmaco-epidemiological studies are those in which at least one patient is enrolled or data collection on patients has begun, but the study report has not yet been finalized. Completed studies are those for which the study report is completed and signed.

No pharmaco-epidemiological studies are ongoing or were completed.

Annex 6 Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part III

Table 14-9 Overview of included protocols

Study title	Protocol status	Version of protocol	Date of protocol version
Not applicable.			

Annex 7 Specific adverse event follow-up forms

Not applicable.

Annex 8 Protocols for proposed and on-going studies in RMP Part IV

Table 14-10 Protocols for proposed and on-going studies in RMP Part IV

Study title	Protocol status	Version of protocol	Date of protocol version
Not applicable			

Annex 9 Newly available study reports for RMP Parts III & IV

This annex presents the study reports or abstracts for RMP Parts III & IV completed since the last Safety Risk Management Plan.

Table 14-11 List of newly available study reports for RMP Parts III & IV

Study code	Date of completion of Clinical Study Report
Not applicable.	

Annex 10 Details of proposed additional risk minimization activities (if applicable)

Not applicable.

Annex 11 Mock-up of proposed additional risk minimization measures (if applicable)

Not applicable.

Annex 12 Other supporting data (including referenced material)

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All old references will be provided upon request.

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