PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for atorvastatin

This is a summary of the risk management plan (RMP) for atorvastatin. The RMP details important risks of atorvastatin, how these risks can be minimised, and how more information will be obtained about atorvastatin's risks and uncertainties (missing information).

Atorvastatin's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how atorvastatin should be used.

Important new concerns or changes to the current ones will be included in updates of atorvastatin's RMP.

I. The Medicine and What It Is Used For

Atorvastatin is authorised for hypercholesterolaemia and prevention of cardiovascular disease (see SmPC for the full indication). Atorvastatin is currently available as film-coated tablets for oral administration containing 10, 20, 40, or 80 mg of atorvastatin and chewable tablets for oral administration containing 5, 10, 20, or 40 mg of atorvastatin. Atorvastatin 5 mg film-coated tablets are available in Japan.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of atorvastatin, together with measures to minimise such risks and the proposed studies for learning more about atorvastatin's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of atorvastatin is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of atorvastatin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of atorvastatin. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

Table 78. List of Important Risks and Missing Information

Important identified risks	Skeletal muscle effects, rhabdomyolysis and rhabdomyolysis-related events Hyperglycaemia, which may require diabetes care in patients with diabetes risk factors Stevens-Johnson syndrome and toxic epidermal necrolysis Concomitant use of coumarin anticoagulants/warfarin Hepatic failure Interstitial lung disease
Important potential risks	Haemorrhagic stroke Autoimmune events
Missing information	Use in paediatric patients < 10 years old

II.B. Summary of Important Risks and Missing Information

Table 79. Summary of Important Risks and Missing Information

Important Identified Risk: Skeletal Muscle Effects, Rhabdomyolysis and Rhabdomyolysis-related Events	
Evidence for linking the risk to the medicine	Clinical trials, literature articles, and post-marketing data
Risk factors and risk groups	Risk factors of atorvastatin related muscle toxicity include concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, azole antifungals, fusidic acid, colchicines, telaprevir, boceprevir, and combination of tipranavir/ritonavir as many of these drugs inhibit cytochrome P450 3A4 metabolism and/or drug-transport and markedly increase the concentration of atorvastatin. A history of renal impairment may also be a risk factor for the development of rhabdomyolysis. Genetic factors such as polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporters such as P-glycoprotein (P-gp) and OATP1B1 (encoded by the SLCO1B1 gene) may also be involved in predisposing towards statin-related muscle adverse events.[75] Other generally recognized pre-disposing risk factors for skeletal muscle AEs include: • Advanced age >80 years old, female gender, low body mass index, Asian descent

Table 79. Summary of Important Risks and Missing Information

	• Concurrent conditions: presence of acute infection, hypothyroidism (untreated or undertreated), impaired renal or hepatic function, biliary tree obstruction, organ transplant recipients, severe trauma, HIV, diabetes mellitus, vitamin D deficiency, hypertension • Surgery with high metabolic demands • History of creatine kinase elevation or of pre-existing/unexplained muscle/joint/tendon pain, inflammatory or inherited metabolic, neuromuscular/muscle defects, previous statin-induced myotoxicity or myopathy while receiving another lipid-lowering therapy[75,76]
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.5, and 4.8; PL sections 2 and 4. Additional risk minimisation measures: None
Important Identified Risk: Hyperglycaemia, Which May Require Diabetes Care in Patients with Diabetes Risk Factors	
Evidence for linking the risk to the medicine	Clinical trials, literature, and post-marketing data
Risk factors and risk groups	The risk of hyperglycaemia requiring diabetes care appears to be limited to patients who are already at high risk for the development of diabetes in the absence of a statin. Analysis of data from TNT, IDEAL, and SPARCL shows that patients at high risk of development of NODM include those with baseline fasting glucose >5.6 mmol/l (100 mg/dl), fasting triglycerides >1.7 mmol/l (150 mg/dl), BMI >30 kg/m2, and a history of hypertension. Patients with none of these risk factors had a risk of 2% or less in each trial, and those with 1 risk factor had a risk of 4% to 5%. Only with 3 or 4 of the risk factors did the risk of new onset T2DM exceed 10%.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, and 4.8; PL sections 2 and 4. Additional risk minimisation measures: None
Important Identified Risk: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis	
Evidence for linking the risk to the medicine	Post-marketing data
Risk factors and risk groups	No specific risk factors have been identified which may predispose patients to develop SJS/TEN as a result of treatment with atorvastatin. Generalised risk factors for SJS/TEN include: certain medications such as anti-gout, anticonvulsants, anti-psychotics, non-steroidal anti-inflammatory drugs and antibiotics, infectious disease processes such as herpes, pneumonia, human immunodeficiency virus (HIV) and Hepatitis A, a weakened immune system, a history or a family history of SJS/TEN and carriers of the HLA-B*1502 gene.[94]
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.8; PL section 4. Additional risk minimisation measures: None
Important Identified Risk: Concomitant Use of Coumarin Anticoagulants/Warfarin	

Table 79. Summary of Important Risks and Missing Information

Evidence for linking the risk to the medicine	Post-marketing data
Risk factors and risk groups	No risk groups or risk factors have been identified at this time in patients receiving atorvastatin. General risk factors of haemorrhagic events include recent haemorrhage, bleeding tendencies due to acquired or congenital disorders of the clotting system, and severe liver disease. General risk factors for venous thromboembolism included trauma or fractures, surgeries, oral contraceptives and hormone replacement therapy, pregnancy and puerperium, hypercoagulability, previous venous thromboembolism, age, bed rest, prolonged travel, metabolic syndrome and air pollution.[97]
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.5; PL section 2. Additional risk minimisation measures: None
Important Identified Risk: Hepatic Failure	
Evidence for linking the risk to the medicine	Clinical trials and post-marketing data
Risk factors and risk groups	Marked elevation of liver enzymes with clinical disease is a rare occurrence with atorvastatin. Hospitalisations for hepatic impairment associated with statin use is estimated at approximately 1 per 1,000 patient-treatment years, while hepatic failure occurs at an estimated incidence of approximately 1 per million patient-treatment years. Long-term safety data indicate that hepatotoxicity tends to occur when a given statin is used at near maximum dose, administered concomitantly with other P450 affecting medications, used in combination with other lipid lowering agents, administered to the elderly or those with renal impairment.[103]
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, and 4.8; PL sections 2 and 4. Additional risk minimisation measures: None
Important Identified Risk: Interstitial Lung Disease	
Evidence for linking the risk to the medicine	Post-marketing data
Risk factors and risk groups	No specific risk factors have been identified which may predispose patients to develop ILD as a result of treatment with atorvastatin. Generalised risk factors for ILD include: connective tissue diseases (e.g. scleroderma, rheumatoid arthritis), primary diseases (e.g. sarcoidosis, pulmonary lymphoma), occupational and environmental diseases (e.g. asbestosis, aluminum oxide fibrosis, Farmer's lung), familial/genetic disorders (e.g. familial idiopathic pulmonary fibrosis, Gaucher's disease), and treatment/drug-induced diseases, as well as bacteria, viruses, and fungi. Numerous medications have also been associated with ILDs, including (but not limited to) antibiotics (penicillins, sulfonamides), anti-inflammatory agents, chemotherapeutic agents (bleomycin, busulfan, cyclophosphamide), narcotics, and select cardiovascular agents such as amiodarone, beta-blockers, and hydrochlorothiazide.[105,106,107]
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. Additional risk minimisation measures:

Table 79. Summary of Important Risks and Missing Information

	None
Important Potential Risk: Haemorrhagic Stroke	
Evidence for linking the risk to the medicine	Limited to a post-hoc analysis of the SPARCL trial
Risk factors and risk groups	Analysis of baseline characteristics in atorvastatin-treated patients from SPARCL revealed that known risk factors for haemorrhagic stroke including age, male gender and high blood pressure were associated with a higher incidence of haemorrhagic stroke. The risk appears to be increased in patients with prior lacunar infarct or prior haemorrhagic stroke.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4; PL section 2. Additional risk minimisation measures: None
Important Potential Risk: Autoimmune Events	
Evidence for linking the risk to the medicine	Post-marketing data
Risk factors and risk groups	There are currently no known risk groups or factors for the development of autoimmune disease in patients receiving atorvastatin. Recognized predisposing risk factors for autoimmune disease include genetic factors as well as environmental insults such as infections, irradiation, and exposure to drugs and toxins.[126]
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8; PL section 2. Additional risk minimisation measures: None
Missing Information: Use in Paediatric Patients < 10 Years Old	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2. Additional risk minimisation measures: None

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of atorvastatin.

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no studies required for atorvastatin.