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 59. List of Important Risks and Missing Information

Important identified risks	Skeletal muscle effects (including immune-mediated necrotizing myopathy), rhabdomyolysis and rhabdomyolysis-related events Hepatic failure
Important potential risks	Haemorrhagic stroke in patients with prior haemorrhagic stroke or lacunar infarct
Missing information	None

II.B. Summary of Important Risks and Missing Information

Table 60. Summary of Important Risks and Missing Information

Important Identified Risk: Skeletal Muscle Effects (Including Immune-Mediated Necrotizing Myopathy), 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.[81] 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 • Concurrent conditions: presence of acute infection, hypothyroidism (untreated or undertreated), impaired renal or hepatic function, biliary tree

Table 60. Summary of Important Risks and Missing Information

	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[81,82] • HMGCR IMNM has one of the strongest associations between an immuno-genetic risk factor and autoimmune disease. The class II HLA allele DRB 1*11: 01 has an OR of 24.5 in whites and 56.5 in blacks.[83] The above finding has been verified in different cohorts from Australia and Japan as well[84,85], which implies that there is probably a different mechanism causing autoimmunity between children and adults that does not involve statin exposure and most likely involve different epitope recognition.[86]
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: 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.[93]
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 Potential Risk: Haemorrhagic Stroke in Patient with Prior Haemorrhagic Stroke or Lacunar Infarct	
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:

Table 60. Summary of Important Risks and Missing Information

	None
Missing Information	
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.