## PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

### VI.1 Elements for summary tables in the EPAR

#### VI.1.1 Summary table of Safety concerns

| | |
|---|---|
| Important identified risks (s) | • Hepatotoxicity<br>• Haemorrhagic stroke<br>• Increased CK levels, skeletal muscle effects, including myopathy and rhabdomyolysis<br>• Interaction with CYP3A4 inhibitors / OATP1B1 inhibitors<br>• Diabetes mellitus<br>• Severe skin reactions<br>• Interstitial lung disease |
| Important potential risks | • Interaction with warfarin<br>• Immune-mediated necrotizing myopathy (IMNM)<br>• Use in pregnancy and lactation |
| Missing information | • Use in pediatric patients < 10 years of age |

#### VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

#### VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.



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### VI.1.4 Summary table of risk minimisation measures

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Important identified risk: Hepatotoxicity | Section 4.2, 4.3, 4.4, 4.8 and 5.3 of Atorvastatin SmPC and corresponding section of PIL have information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | None proposed |
| Important identified risk: Haemorrhagic stroke | Section 4.4 and 5.1 of Atorvastatin SmPC has information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | None proposed. |
| Important identified risk: Increased CK levels, skeletal muscle effects, including myopathy and rhabdomyolysis | Section 4.4, 4.5, 4.8 and 4.9 of Atorvastatin SmPC and corresponding section of PIL have information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | None proposed. |
| Important identified risk: Interaction with | Section 4.4, 4.5 and 5.2 of Atorvastatin SmPC and corresponding section of PIL | None proposed. |


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| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|
| CYP3A4 inhibitors / OATP1B1 inhibitors | have information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | |
| Important identified risk: Diabetes mellitus | Section 4.4 and 4.8 of Atorvastatin SmPC and corresponding section of PIL have information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | None proposed. |
| Important identified risk: Severe skin reactions | Section 4.8 of Atorvastatin SmPC and corresponding section of PIL have information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | None proposed. |
| Important identified risk: Interstitial lung disease | Section 4.4 and 4.8 of Atorvastatin SmPC has information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | None proposed. |


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| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|
| Important potential risk: Interaction with warfarin | Section 4.5 of Atorvastatin SmPC and corresponding section of PIL have information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | None proposed. |
| Important potential risk: Immune-mediated necrotizing myopathy (IMNM) | Section 4.4 and 4.8 of Atorvastatin SmPC has information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | None proposed. |
| Important potential risk: Use in pregnancy and lactation | Section 4.3, 4.6 and 5.3 of Atorvastatin SmPC and corresponding section of PIL have information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the product. | None proposed. |
| Missing information: Use in pediatric patients < 10 years of age | Section 4.2, 4.4, 4.8 and 5.1 of Atorvastatin SmPC and corresponding section of PIL have information on this safety concern.<br>Other routine risk minimisation measures including the prescription only status of the | None proposed. |


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| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | product. | |

## VI.2 Elements for a public summary

### VI.2.1 Overview of disease epidemiology

Hypercholesterolaemia (High cholesterol levels in blood)

People with high blood cholesterol levels have a greater risk of having a heart attack, stroke (occurs due to problems with the blood supply to the brain) or other related cardiovascular (heart and blood vessel) disease. This is because cholesterol and other fatty substances (lipids) may build up on the inside wall of blood vessels causing them to narrow. Sometimes blood clots form which block the blood vessels completely. Cardiovascular diseases such as strokes and heart attacks cause almost 1 in 3 deaths worldwide each year. High cholesterol levels are common throughout the world, but are more common in high income than low-income regions. In high-income regions such as Europe, the United States, Canada and Japan, more than half of adults have high cholesterol levels. Sometimes cholesterol levels can be lowered with changes in diet and increased exercise. However, cholesterol levels are often affected by things that cannot be changed, such as age, sex, or family history. Cholesterol levels usually rise steadily with age, but stabilise after middle age.

### VI.2.2 Summary of treatment benefits

Hypercholesterolaemia

In this study, different dosages of atorvastatin were given to patients with high cholesterol to evaluate cholesterol level. Total 81 patients were assigned to receive dummy medication or 2.5,


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5, 10, 20, 40, or 80 mg atorvastatin once daily for 6 weeks. Plasma low density cholesterol reductions from baseline were dose related, with 25% to 61% reduction from the minimum dose to the maximum dose of 80 mg atorvastatin once a day. In this study, atorvastatin was well tolerated by patients with high cholesterol, had an acceptable safety profile, and provided greater reduction in cholesterol when compared to dummy medication.

Prevention of cardiovascular disease

The effect of atorvastatin on fatal and non-fatal heart disease was assessed in a study in which 40-79 years of age patients with high blood pressure and no previous heart disease treatment were included. Patients were treated with either atorvastatin 10 mg daily (n=1,428) or dummy medication (n=1,410). All patients had at least 3 of the pre-defined heart risk factors: male gender, age ≥55 years, smoking, high sugar level in blood, history of heart disease in a first-degree relative and circulation disorders that affect blood vessels outside of the heart and brain. Atorvastatin significantly reduced the risk of developing cardiovascular disease when compared to dummy treatment (placebo).

### VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of atorvastatin in children younger than 6 years has not been established. There is limited experience in children between 6-10 years of age.

Safety of atorvastatin in pregnant women has not been established.

### VI.2.4 Summary of safety concerns

**Important identified risks:**

| **Risk** | **What is known** | **Preventability** |
|---|---|---|
| Liver problems | People taking atorvastatin | Talk to your doctor, |


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| Risk | What is known | Preventability |
|---|---|---|
| (Hepatotoxicity) | uncommonly (may affect up to 1 in 100 people) developed hepatitis (liver inflammation).<br>People taking atorvastatin very rarely (may affect up to 1 in 10,000 people) experienced unexpected or unusual bleeding or bruising, this may be suggestive of a liver complaint. | pharmacist or nurse before you take atorvastatin, if you have a history of liver disease.<br>Do not take atorvastatin if you have or ever had a disease which affects the liver or had any unexplained abnormal blood tests for liver function. |
| Rupture in a weakened blood vessel in the brain (Haemorrhagic stroke) | After the experiment, data concluded that atorvastatin 80 mg reduced the incidence of ischemic stroke (an obstruction within a blood vessel supplying blood to the brain) and increased the incidence of hemorrhagic stroke (a weakened blood vessel leak).<br>The risk of hemorrhagic stroke was increased in patients who entered the study with prior lacunar infarct (occlusion of one of the penetrating arteries that provides blood to the brain's deep structures), but the risk of ischemic stroke (an obstruction within a blood vessel supplying blood to the brain) was also decreased in these | Your doctor will monitor you while you are taking this medicine.<br>A risk of hemorrhagic stroke (a weakened blood vessel leak) should be carefully considered before initiating atorvastatin treatment. |


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| Risk | What is known | Preventability |
|---|---|---|
| | patients. | |
| Increased creatine kinase (CK) level, skeletal muscle effects including muscle aches and pains as a symptom of a muscle damage (Increased CK levels, skeletal muscle effects, including myopathy and rhabdomyolysis) | People taking atorvastatin rarely (may affect up to 1 in 1000 people) experienced muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown does not always go away, even after you have stopped taking atorvastatin and it can be life-threatening and lead to kidney problems.<br><br>People taking atorvastatin commonly (may affect up to 1 in 10 people) developed muscle pain and increase in blood creatine kinase.<br><br>People taking atorvastatin uncommonly (may affect up to 1 in 100 people) developed muscle fatigue.<br><br>People taking atorvastatin had developed muscle weakness that is constant with unknown frequency.<br><br>If you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using | Talk to your doctor, pharmacist or nurse before you take atorvastatin, if you have had repeated or unexplained muscle aches or pains, a personal history or family history of muscle problems and also have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other statin or fibrate medicines).<br><br>Tell your doctor, pharmacist or nurse if you have a muscle weakness that is constant. Additional tests and medicines may be needed to diagnose and treat this.<br><br>Doctor will need to carry out a blood test before and possibly during your atorvastatin treatment alone or with certain medicines to predict your risk of muscle related side effects and |



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| Risk | What is known | Preventability |
|---|---|---|
| | atorvastatin medicine. Your doctor will tell you when it is safe to restart atorvastatin. Taking atorvastatin with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis). | increase in blood creatine kinase.<br>Tell your doctor and pharmacist if you are taking or have taken in the last 7 days a medicine called fusidic acid, (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and Atorvastatin tablets can lead to serious muscle problems (rhabdomyolysis). |
| Interaction with certain medications (medications which inhibits or arouse the actions of enzyme CYP3A4 /OATP1B1) | The risk of muscle related side effects e.g muscle pain, rhabdomyolysis (breakdown of muscle tissue that leads to the release of muscle fiber contents into the blood) is known to increase when certain medicines are taken at the same time.<br>Below are some medicines that may change the effect of atorvastatin or their effect may be changed by atorvastatin. This type of interaction could make one or both of the | Doctor will need to carry out a blood test before and possibly during your atorvastatin treatment alone or with certain medicines to predict your risk of muscle related side effects.<br>In the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients |



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| Risk | What is known | Preventability |
|---|---|---|
| | medicines less effective.<br>Potent inhibitors and inducer of CYP3A4 or transport proteins:<br>Example: erythromycin, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole, rifampin, fusidic acid. | is recommended. |
| High levels of sugar in blood (Diabetes mellitus) | You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.<br>People taking atorvastatin commonly (may affect up to 1 in 10 people) developed increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels).<br>Possible side effect such as diabetes is reported with some statins. | While you are taking atorvastatin, your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes.<br>Doctor will need to carry out a blood test before and possibly during your atorvastatin treatment to predict your sugar level. |
| Severe skin reactions | People taking atorvastatin rarely (may affect up to 1 in 1000 people) experienced serious illness with severe peeling and swelling of the skin, | If you experience severe skin reactions, stop taking your tablets and tell your doctor immediately or go to the |


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| Risk | What is known | Preventability |
|---|---|---|
| | blistering of the skin, mouth, eyes genitals and fever. Skin rash with pink-red blotches especially on palms of hands or soles of feet which may blister.<br>People taking atorvastatin uncommonly (may affect up to 1 in 100 people) developed rash, skin rash and itching and hives. | nearest hospital accident and emergency department. |
| Inflammation of the lungs causing breathing problems including persistent cough and/or shortness of breath or fever (Intestinal lung disease) | People taking atorvastatin had developed interstitial lung disease in exceptional cases especially with long term therapy. Presenting features can include dyspnoea (breathing problems), non-productive cough and deterioration in general health (fatigue, weight loss and fever). | If patient has developed interstitial lung disease (Inflammation of the lungs causing breathing problems including persistent cough and/or shortness of breath or fever), atorvastatin therapy should be discontinued. |

**Important potential risks**

| Risk | What is known |
|---|---|
| Interaction with warfarin | Warfarin (medicine which reduces blood clotting) interact with atorvastatin may change the effect of atorvastatin or its effect may be changed by atorvastatin. This type of interaction could make one or both of the medicines less effective.<br>Please tell your doctor, pharmacist or nurse if you are taking or |



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| Risk | What is known |
|---|---|
| | have recently taken warfarin (which reduces blood clotting). |
| Muscle weakness caused by an autoimmune response (Immune-mediated necrotizing myopathy (IMNM)) | People taking atorvastatin had developed muscle weakness caused by an autoimmune response with unknown frequency.<br>There have been very rare reports of muscle weakness caused by an autoimmune response during or after treatment with some statins. Immune-mediated necrotizing myopathy (IMNM) (atorvastatin induced autoimmune response) characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of atorvastatin treatment. |
| Use in pregnancy and lactation | The safety of atorvastatin during pregnancy and breast-feeding has not yet been proven. Ask your doctor, pharmacist or nurse for advice before taking atorvastatin.<br>Do not take atorvastatin if you are pregnant, trying to become pregnant or you are able to become pregnant unless you use reliable contraceptive measures.<br>Do not take atorvastatin if you are breast-feeding. |

**Missing information**

| Risk | What is known |
|---|---|
| Use in pediatric patients < 10 years of age | There is limited experience in children between 6-10 years of age. Atorvastatin is not indicated in the treatment of patients below the age of 10 years. |


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| Risk | What is known |
|---|---|
| | Developmental safety in the paediatric population has not been established. |

### VI.2.5 Summary of additional risk minimisation 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 minimising 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 minimisation measures.

This medicine has no additional risk minimisation measures.

### VI.2.6 Planned post authorisation development plan

No studies planned.

### VI.2.7 Summary of changes to the risk management plan over time

| Version | Date | Safety Concern | Comment |
|---|---|---|---|
| 2.0 | 04 July 2016 | This RMP has been updated with below safety concerns:<br>Important identified risks (s): • Hepatotoxicity • Haemorrhagic stroke • Increased CK levels, skeletal muscle | The RMP has been updated based on RMS Day 70 and CMS Day 100 Preliminary assessment report (AT/H/0667/001-004/DC) of Atorvastatin. |



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| Version | Date | Safety Concern | | Comment |
|---|---|---|---|---|
| | | | effects, including myopathy and rhabdomyolysis<br>• Interaction with CYP3A4 inhibitors / OATP1B1 inhibitors<br>• Diabetes mellitus<br>• Severe skin reactions<br>• Interstitial lung disease | |
| | | Important potential risks | • Interaction with warfarin<br>• Immune-mediated necrotizing myopathy (IMNM)<br>• Use in pregnancy and lactation | |
| | | Missing information | • Use in pediatric patients < 10 years of age | |


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