sRMP

Atorvastatin Medical Valley

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

This product is indicated for the lowering of cholesterol blood levels and the prevention of events in the heart and blood vessels.

Ischaemic heart disease (IHD), a condition in which the supply of blood to the heart is reduced, is the leading cause of death world-wide. The most important risk factors for IHD are raised body mass index (the measure of weight compared to height), high blood pressure, high cholesterol level in blood and smoking.

The results of a study, which combined data from other 17 studies that included a total of about 55,000 patients, showed that an increase in levels of lipids in blood was associated with increased risk of disease of the heart and blood vessels both in men and women. When a variety of other risk factors were taken into account, the relative risks were decreased but were still statistically significant. Therefore, this study demonstrated that increased levels of lipids in blood are a risk factor of cardiovascular disease.

VI.2.2 Summary of treatment benefits

The lipid-lowering efficacy of atorvastatin in patients with increased blood cholesterol levels due to inherited genetic abnormalities (primary hypercholesterolaemia) is well-established. The drug consistently reduces total and LDL-cholesterol ("the bad cholesterol") levels in serum in a dose-dependent manner, with atorvastatin 10, 20, 40 and 80 mg/day producing reductions in serum LDL-cholesterol levels of 35 to 42%, 42 to 44%, 50 and 59 to 61%, respectively, in various studies in which effects of atorvastatin were compared to a control group receiving treatment with no real effect and in studies done without a control group.

VI.2.3 Unknowns relating to treatment benefits

The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Increased transaminases, hepatitis, jaundice (Hepatotoxicity)	Atorvastatin is known to cause a liver injury and is therefore contraindicated in patients with liver disease. Atorvastatin should be used with caution in patients who consume high amounts of alcohol and/or have a history of liver disease as the risk of liver injury is increased in such	**What you need to know before you take Atorvastatin** Do not take Atorvastatin if you have had any unexplained abnormal blood tests for liver function or if you have had any unexplained abnormal blood tests for liver function. Talk to your doctor, pharmacist or nurse before taking Atorvastatin.

Risk	What is known	Preventability
	patients. Patients with disease which affects the liver or any unexplained abnormal blood tests for liver function should not take atorvastatin, while atorvastatin should be used with precaution in patients with history of liver disease or regularly drink a large amount of alcohol. It is important patients to be aware of the risk of experiencing hepatic failure as it has been described as very rare side effect and inform their doctor if they experience any of the symptoms of hepatic failure. Medicines such as atorvastatin may be associated with hepatic failure. Hepatic failure is marked by: - Jaundice. - Bleeding easily. - Swollen abdomen. - Mental disorientation or confusion (known as hepatic encephalopathy) - Sleepiness. - Coma.	Talk to your doctor or pharmacist before taking Atorvastatin: -if you regularly drink a large amount of alcohol -if you have a history of liver disease **Warnings and precautions** The following are reasons why Atorvastatin may not be suitable for you: if you have a history of liver disease or if you regularly drink a large amount of alcohol. **Other possible side effects with Atorvastatin:** Common side effects (may affect up to 1 in 10 people) include: hepatitis (liver inflammation). Rare side effects (may affect up to 1 in 1,000 people) include: cholestasis (yellowing of the skin and whites of the eyes). Very rare (may affect up to 1 in 10,000 people): If you experience problems with unexpected or unusual bleeding or bruising, this may be suggestive of a liver complaint. You should consult your doctor as soon as possible. Liver function tests should be performed before the initiation of treatment and periodically thereafter.
Bleeding (haemorrhage) that suddenly interferes with the brain's function (Haemorrhagic stroke)	Heamorrhagic stroke was increased in patients with a recent stroke or transient ischemic attack.	**Warnings and precautions** Talk to your doctor, pharmacist or nurse before taking Atorvastatin. The following are reasons why Atorvastatin may not be suitable for you: − if you have had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes

Severe potentially fatal disease that destroys skeletal muscle (Rhabdomyolysis, myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia)	Some people may experience muscle disorders, namely myopathy/rhabdomyolysis/immune necrotizing myopathy after receiving atorvastatin with symptoms such as: muscle aches and pain (myalgia), stiffness, and muscle weakness (especially common with severe muscle damage). Rhabdomyolysis may cause a darkening of the urine colour. Myoglobin is released from the muscles when they break down and is excreted into the urine. This can cause a red or cola colour of the urine.	**Warnings and precautions** Talk to your doctor, pharmacist or nurse before taking Atorvastatin. The following are reasons why Atorvastatin may not be suitable for you: − if you have had repeated or unexplained muscle aches or pains, a personal history or family history of muscle problems − if you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other '-statin' or '-fibrate' medicines) If any of these apply to you, your doctor will

Risk	What is known	Preventability
		need to carry out a blood test before and possibly during your Atorvastatin treatment to predict your risk of muscle related side effects. The risk of muscle related side effects e.g. rhabdomyolysis is known to increase when certain medicines are taken at the same time (see Section 2 "Other medicines and Atorvastatin"). Also tell your doctor or pharmacist if you have a muscle weakness that is constant. Additional tests and medicines may be needed to diagnose and treat this. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. There 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 medicines less effective. Alternatively it could increase the risk or severity of side-effects, including the important muscle wasting condition known as rhabdomyolysis described in Section 4: − Medicines used to alter the way your immune system works, e.g. ciclosporin − Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole, rifampin, fusidic acid − Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, colestipol − Some calcium channel blockers used for angina or high blood pressure, e.g. amlodipine, diltiazem,; medicines to regulate your heart rhythm e.g. digoxin, verapamil, amiodarone − Medicines used in the treatment of HIV e.g. ritonavir, lopinavir, atazanavir, indinavir, darunavir, the combination of tipranavir/ritonavir etc. − Some medicines used in the treatment of hepatitis C e.g. telaprevir − Other medicines known to interact with Atorvastatin include ezetimibe (which lowers cholesterol), warfarin (which reduces blood clotting), oral contraceptives, stiripentol (an anti-convulsant for epilepsy), cimetidine (used for heartburn and peptic ulcers), phenazone (a painkiller), colchicine (used to treat gout), antacids (indigestion products containing aluminium or magnesium) and boceprevir (used to treat liver disease such as hepatitis C) − Medicines obtained without a prescription: St John's Wort Please tell your doctor or pharmacist if you

Risk	What is known	Preventability
		are taking or have recently taken any other medicines, including medicines obtained without a prescription. If you experience any of the following serious side effects, stop taking your tablets and tell your doctor immediately or go to the nearest hospital accident and emergency department. Rare: may affect up to 1 in 1,000 people 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. The 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.
Interaction with other medicines (Interaction with CYP3A4 inhibitors / OATP1B1 inhibitors)	These types of medicines can increase the levels of atorvastatin.	**Other medicines and Atorvastatin** Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. There 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 medicines less effective. Alternatively it could increase the risk or severity of side-effects. Medicines used to alter the way your immune system works, e.g. ciclosporin. Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole, rifampin, fusidic acid. Medicines used in the treatment of HIV e.g. ritonavir, lopinavir, atazanavir, indinavir, darunavir, the combination of tipranavir/ritonavir etc.
Severe skin reactions	Some people may experience severe skin reactions, namely dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis after receiving atorvastatin.	**Possible side effects** **Rare** (may affect up to 1 in 1, 000 people) -Serious illness with severe peeling and swelling of the skin, blistering of the skin, mouth, eyes, genitals and fever. Skin rash with pink-red blotches (uneven patch of colour) especially on palms of hands or soles of feet which may blister.
Diabetes mellitus	Atorvastatin therapy may be associated with increases in blood sugar levels (common side effect) or diabetes (very rare side effect). Patients are likely to be at risk of developing diabetes if they have high	**Warnings and precautions** While patients are on this medicine their doctor will monitor them closely if they have diabetes or are at risk of developing diabetes. If patient have diabetes their doctor will continue careful to monitor blood sugar

Risk	What is known	Preventability
	levels of sugars and fats in your blood, are overweight and have high blood pressure.	levels. **Possible side effects** **Common** (may affect up to 1 in 10 people): - increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels), Possible side effects reported with some statins (medicines of the same type): **Very rare** (may affect up to 1 in 10,000 people): - Diabetes. This is more likely if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure. Your doctor will monitor you while you are taking this medicine.
Lung disease causing progressive scarring of lung tissue (interstitial lung disease)	Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever).	**Warnings and precautions** Talk to your doctor or pharmacist before taking Atorvastatin It is especially important to check with your doctor or pharmacist before taking Atorvastatin if you have severe respiratory failure. Possible side effects reported with some statins (medicines of the same type): - breathing problems including persistent cough and/or shortness of breath or fever.

Important potential risks

Risk	What is known	Preventability
Use during pregnancy and breastfeeding	Safety in pregnant and lactation women have not been established. Animal studies showed toxicity to reproduction.	**Pregnancy, breast-feeding and fertility** If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not take Atorvastatin if you are pregnant, or if you are trying to become pregnant. Do not take Atorvastatin if you are able to become pregnant (you are fertile) unless you use reliable contraceptive measures. Do not take Atorvastatin if you are breast-feeding.

Important missing information

Risk	What is known
Use in paediatric 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.

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.
The SmPC and the PL for Atorvastatin can be found in the national authority's web page. This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable

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

Version	Date	Safety Concern	Comment
1.1	02-Jun-2016	*Following safety concerns are added or changed:* **Important identified risks:** - Hepatotoxicity (increased transaminases, hepatitis, jaundice) - Haemorrhagic stroke - Rhabdomyolysis, myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia - Interaction with CYP3A4 inhibitors/ OATP1B1 inhibitors - Diabetes mellitus - Severe skin reactions - Interstitial lung disease **Important potential risks:** - Use during pregnancy and breastfeeding **Important missing information:** - Use in paediatric patients <10 years of age	This RMP has been updated according to DK/H/2592/01-04/DC assessment report.