Lipistad 10 mg film-coated tablets,
Lipistad 20 mg film-coated tablets
Lipistad 40 mg film-coated tablets
Lipistad 80 mg film-coated tablets

27.11.2015, Version V1.2

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

Lipistad 10 mg film-coated tablets,

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VI.2.1 Overview of disease epidemiology

According to the Guideline on good pharmacovigilance practices (GVP) Module V "Risk management systems", V.C.3.1.a, RMP Part II module I may be omitted for generic products.

VI.2.2 Summary of treatment benefits

[product name] contains the active substance atorvastatin which belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.

[product name] is used to lower lipids known as cholesterol and triglycerides in the blood when a low fat diet and life style changes on their own have failed. If you are at an increased risk of heart disease, [product name] can also be used to reduce such risk even if your cholesterol levels are normal. You should maintain a standard cholesterol lowering diet during treatment.

In a dose-response study, patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus, atorvastatin has been shown to consistently reduce concentrations of certain types of fats (total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B and triglycerides), while producing variable increases in other fats (high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1).
Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk of problems related to the cardiovascular (heart and blood vessels) system.

<u>Homozygous familial hypercholesterolaemia</u>
In a compassionate-use study on 335 patients, 89 patients were identified to have homozygous familial hypercholesterolaemia. In those 89, the mean percent reduction in LDL-C was approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

<u>Atherosclerosis</u>
In the Reversing Atherosclerosis with Aggressive Lipid- Lowering Study (REVERSAL), the effect of lipid (fat) lowering therapy with atorvastatin 80mg and pravastatin 40mg were compared in respect to their impact on coronary atherosclerosis (thickening of the walls of blood vessels of the heart) in patients with coronary heart disease. In the 253 patients treated with atorvastatin, atherosclerosis did not get worse. Additionally, the mean size of atheroma (an accumulation of material in the artery walls that reduces the artery lumen)

decreased in the atorvastatin group, while an increase was noted in patients treated with pravastatin; this difference was statistically significant. Atorvastatin also reduced the level of different lipid levels (LDL cholesterol, total cholesterol and apolipoprotein B) significantly more than pravastatin.
Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower dose strengths.

The safety and tolerability profiles of the two treatment groups were comparable.

Acute coronary syndrome
In the MIRACL study, 3,086 patients with an acute coronary syndrome received either atorvastatin 80mg or placebo. Treatment was initiated during the acute phase after hospital admission and lasted for 16 weeks. Treatment with atorvastatin 80 mg/day reduced the risk of death from any cause, nonfatal heart attack, resuscitated heart arrest, or angina pectoris with evidence of myocardial ischaemia (lack of oxygen in the heart muscle) requiring hospital admission, by 16%. This was mainly due to a 26% reduction in re-hospitalisation for angina pectoris with evidence of myocardial ischaemia (p=0.018).

Prevention of cardiovascular disease
The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). The study included patients between 40 and 79 years with high blood pressure (hypertension), who never had a heart attack or been treated for angina, but had at least three risk factors for cardiovascular disease[1] and had total cholesterol (TC) levels of 251 mg/dl. In addition to their blood pressure medication, the patients also received either daily atorvastatin 10mg or a placebo. A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group).
The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without a prior history of cardiovascular disease. All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy (inflammation of retina in the eye) or microalbuminuria (moderate increase in the level of urine albumin). A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group).

Recurrent stroke
In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years), and had an average baseline LDL cholesterol of 133 mg/dL (3.4 mmol/L). Atorvastatin 80 mg reduced the risk of fatal or non-fatal stroke by 15% compared to placebo. All cause mortality was 9.1% (216/2365) for atorvastatin versus 8.9% (211/2366) for placebo. In a later analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (occurs as a result of an obstruction within a blood vessel supplying blood to the brain) and increased the incidence of hemorrhagic stroke (occurs when a weakened blood vessel ruptures) compared to placebo.
The risk of hemorrhagic stroke was increased in patients who entered the study with prior hemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo), and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo).

[1] male gender, age >55 years, smoking, diabetes, history of coronary heart disease in a first-degree relative, a total cholesterol: high-density lipoprotein cholesterol radio of >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria

The risk of hemorrhagic stroke was increased in patients who entered the study with prior lacunar infarct (type of stroke that results from occlusion of one of the penetrating arteries that provides blood to the brain's deep structures) (20/708 for atorvastatin versus 4/701 for placebo), but the risk of ischemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive atorvastatin 80 mg/day.

All-cause mortality was 15.6% (7/45) for atorvastatin versus 10.4% (5/48) in the subgroup of patients with prior hemorrhagic stroke. All-cause mortality was 10.9% (77/708) for atorvastatin versus 9.1% (64/701) for placebo in the subgroup of patients with prior lacunar infarct.

Paediatric Population

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 6-17 years old

An 8-week, open-label study (a type of clinical trial in which both the researchers and participants know which treatment is being administered) to evaluate certain drug properties, safety and tolerability of atorvastatin was conducted in children and adolescents with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL cholesterrol ≥ 4 mmol/L. A total of 39 children and adolescents, 6 to 17 years of age, were enrolled. Group A included 15 children, 6 to 12 years of age and at Tanner Stage 1 (a scale of physical development in children, adolescents and adults). Group B included 24 children, 10 to 17 years of age and at Tanner Stage ≥ 2.

The initial dose of atorvastatin was 5 mg daily of a chewable tablet in Group A and 10 mg daily of a tablet formulation in Group B. The atorvastatin dose was permitted to be doubled if a subject had not attained target LDL cholesterol of < 3.35 mmol/L at Week 4 and if atorvastatin was well tolerated.

Mean values for LDL cholesterol, total cholesterol, VLDL-cholesterol, and Apolipoprotein B decreased by Week 2 among all subjects. For subjects whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first assessment, after dose escalation. The mean percent decreases in lipid parameters were similar for both groups, regardless of whether subjects remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-cholesterol and total cholesterol was approximately 40 % and 30 %, respectively, over the range of exposures.

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 10-17 years old

In a study, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (FH) or severe hypercholesterolaemia were randomised to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and increase to 20 mg if the LDL-C level was >3.36 mmol/L. Atorvastatin significantly decreased plasma levels of total cholesterol, LDL-cholesterol, triglycerides, and apolipoprotein B during the 26 week double-blind phase (an experimental procedure in which neither the subjects of the experiment nor the persons administering the experiment know the critical aspects of the experiment). The mean achieved LDL-cholesterol value was 3.38 mmol/L (range: 1.81-6.26 mmol/L) in the atorvastatin group compared to 5.91 mmol/L (range: 3.93-9.96 mmol/L) in the placebo group during the 26-week double-blind phase.

An additional paediatric study of atorvastatin versus colestipol in patients with hypercholesterolaemia aged 10-18 years demonstrated that atorvastatin caused a significant reduction in LDL-C at week 26 compared with colestipol.

A compassionate use study (refers to the use of an investigational drug outside of a clinical trial by patients with serious or life-threatening conditions who do not meet the enrollment criteria for the clinical trial in progress) in patients with severe hypercholesterolaemia (including homozygous hypercholesterolaemia) included 46 paediatric patients treated with

atorvastatin increased gradually according to response (some subjects received 80 mg atorvastatin per day). The study lasted 3 years: LDL-cholesterol was lowered by 36 %.

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

VI.2.3 Unknowns relating to treatment benefits

Only limited data are available on safety and efficacy of atorvastatin in homozygous familial hypercholesterolaemia.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Liver disorders, including hepatitis and increased laboratory values (Hepatotoxicity (increased transaminases, hepatitis, jaundice))	An abnormal liver function detected on blood test results may affect up to 1 in 10 people treated with [product name]. Hepatitis (inflammation of the liver) may affect up to 1 in 100 people during treatment with [product name]. Bleeding or bruising associated with a liver complaint have very rarely occurred and may affect up to 1 in 10 000 people.	**DO NOT take [product name]** if you have or have ever had a disease which affects the liver, or if you have had any unexplained abnormal blood tests for liver function. Talk to your doctor, pharmacist or nurse **before taking [product name]** if you are unsure. They will advise if treatment with [product name] is suitable for you: **Consult your doctor as soon as possible** if you experience yellowing of your skin or eyes, or problems with unexpected or unusual bleeding or bruising while receiving [product name]; this may be suggestive of a liver complaint.
Disorders affecting the muscles, including pain, inflammation and muscle break-down, as well as increased laboratory values (Rhabdomyolysis, myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia)	[product name] and other drugs of its class may in rare occasions affect the skeletal muscle (may affect up to 1 in 1 000 people). Muscle weakness, tenderness or pain, particularly in combination with feeling unwell or a high temperature, may be caused by an abnormal muscle breakdown which can be life-threatening and lead to kidney problems.	**If you experience muscle pain, cramps or weakness especially if accompanied by malaise or fever, or if you have dark-coloured urine, stop taking your tablets and tell your doctor immediately or go to the nearest hospital accident and emergency department.** Several conditions may predispose you to

		rhabdomyolysis. Tell your doctor **before starting treatment with [product name]** if any of these apply to you in the past or at the moment: • problems affecting your muscles (including those occurring in your family and those caused by drugs) • impaired kidney function • impaired thyroid function • liver problems • consumption of substantial quantities of alcohol • age over 70 years
Interactions with drugs inhibiting a certain enzyme, and with other drugs (Interaction with CYP3A4 inhibitors)	Certain medicinal products may increase the plasma concentration of atorvastatin; these include potent inhibitors of a certain enzyme (CYP3A4) or transport proteins (examples are some antibiotics, antivirals). If these drugs are taken at the same time as [product name], the risk of adverse effects, especially rhabdomyolysis (see above) is increased.	Tell your doctor or pharmacist before starting therapy with [product name] if you are taking any other medications or dietary supplements, even if they have not been prescribed to you. They will let you know if it is safe for you to take [product name] with your other medications, they might lower your dosage of [product name] or recommend a different therapy.
Sleep problems (Sleep disturbances (incl. insomnia and nightmares))	Sleep problems, such as insomnia and nightmares have been reported in up to 1 in a 100 patients.	Tell your doctor or pharmacist before starting therapy with [product name] if you have or have ever had long-term sleep problems. Tell your doctor or pharmacist if you experience any sleep disturbances whilst on [product name] treatment.
Diabetes (Diabetes mellitus)	Some evidence suggests that statins (drugs of the class that [product name] belongs to) raise blood sugar levels. In patients at high risk of future diabetes, treatment may be necessary. However,	Tell your doctor or pharmacist before starting therapy with [product name] if you have or have ever had problems with your blood sugar.

	the risk of diabetes usually does not outweigh the benefits of statins in reducing blood lipid levels and thereby preventing other problems, such as heart attack. Risk factors include baseline fasting blood glucose levels, obesity, raised blood lipids and high blood pressure.	Tell your doctor or pharmacist if you experience any of the following: Urinating often • Feeling very thirsty • Feeling very hungry - even though you are eating • Extreme fatigue • Blurry vision • Weight loss
Simultaneous use with warfarin (a blood-thinner) (Concomitant use of warfarin)	In a clinical study in patients receiving chronic warfarin (blood-thinner) therapy, simultaneous administration of atorvastatin 80 mg daily with warfarin caused a small increase in bleeding risk during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. However, only very rare cases of clinically significant interactions have been reported.	Tell your doctor or pharmacist before starting therapy with [product name] if you are taking a blood-thinner. Your doctor will perform regular blood test if you are simultaneously taking [product name] and a blood-thinner. Tell your doctor or pharmacist if you experience any of the following: • Unexplained bruising • Persistent nausea, stomach upset, or vomiting blood • Headaches, dizziness, or weakness • Nosebleeds • Dark red or brown urine • Dark-colored stools
Severe skin reactions	Severe skin reactions, such as erythema multiforme, Stenens-Johnson syndrome and toxic epidermal necrolysis have rarely been reported with atorvastatin (between 1 in 100 patients and 1 in 10,000 patients).	Tell your doctor or pharmacist if you experience any of the following: • Facial swelling • Tongue swelling • Hives • Skin pain • A red or purple skin rash that spreads within hours to days • Blisters on your skin and the mucous membranes of your

		mouth, nose, eyes and genitals • Shedding of your skin • Fever
Peripheral nerve damage (Polyneuropathy)	Rare cases of peripheral nerve damage, manifesting itself as weakness, numbness and pain in hands and feet, have been reported with atorvastatin (between 1 in 100 patients and 1 in 10,000 patients).	Tell your doctor or pharmacist if you experience any of the following: • Gradual onset of numbness and tingling in feet or hands • Sharp, burning pain • Extreme sensitivity to touch • Lack of coordination and falling

Important potential risks

Risk	**What is known** **(Including reason why it is considered a potential risk)**
Interstitial lung disease	Cases of lung disorders affecting the interstitium have been observed with the class of drugs that [product name] belongs to, especially when the drug had been taken for a long time. Symptoms can include shortness of breath, non-productive cough and deterioration in general health (fatigue, weight loss and fever).
Sexual dysfunction	Sexual dysfunction (e.g. erectile dysfunction) has been reported with some statins. A causal relationship cannot be clearly established.
Cognitive impairment	Cognitive (brain-related) impairment, such as memory loss, forgetfulness and confusion, has been reported by some statin users. A causal relationship cannot be clearly established.
Bleeding in the brain in patients that have had a stroke or short-term loss of blood flow in the brain (Haemorrhagic stroke)	Patients who had recently had a stroke or transient ischaemic attack (loss of blood flow in the brain) more frequently experienced bleeding into the brain if they were treated with atorvastatin than if they received a placebo, according to a post-hoc analysis.

Missing information

Risk	**What is known**
Use during pregnancy and lactation	Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been

	conducted in pregnant women. Rare reports of birth defects following exposure to statins in the womb have been received. Animal studies have shown toxicity to reproduction. It is not known whether atorvastatin or its breakdown products are excreted in human milk. In animal studies, plasma concentrations were similar to those in milk. Because of the potential for serious adverse reactions, women taking atorvastatin should not breast-feed their infants.
Use in children younger than 10 years	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 risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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 post-authorisation studies have been imposed or are planned.

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

Not applicable