SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

LIPITOR® 10 tablets

LIPITOR® 20 tablets

LIPITOR® 40 tablets

LIPITOR® 80 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LIPITOR 10: Each tablet contains atorvastatin calcium trihydrate, equivalent to 10 mg atorvastatin.

LIPITOR 20: Each tablet contains atorvastatin calcium trihydrate, equivalent to 20 mg atorvastatin.

LIPITOR 40: Each tablet contains atorvastatin calcium trihydrate, equivalent to 40 mg atorvastatin.

LIPITOR 80: Each tablet contains atorvastatin calcium trihydrate, equivalent to 80 mg atorvastatin.

Contains sugar (lactose monohydrate).

Excipients with known effect

Each LIPITOR 10 tablet contains 32,80 mg lactose monohydrate.

Each LIPITOR 20 tablet contains 65,61 mg lactose monohydrate.

Each LIPITOR 40 tablet contains 131,22 mg lactose monohydrate.

Each LIPITOR 80 tablet contains 262,44 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

LIPITOR 10: A white, elliptical, film-coated tablet, debossed with ‘10’ on one side and ‘VLE 155’ on the other side.

LIPITOR 20: A white, elliptical, film-coated tablet, debossed with ‘20’ on one side and ‘VLE 156’ on the other side.

LIPITOR 40: A white, elliptical, film-coated tablet, debossed with ‘40’ on one side and ‘VLE 157’ on the other side.

LIPITOR 80: A white, elliptical, film-coated tablet, debossed with '80' on one side and 'VLE 158' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

LIPITOR is indicated:

- As an adjunct to diet for reduction of elevated total-cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B and triglycerides (TG) levels and to moderately increase HDL-cholesterol (HDL-C) in patients with primary hypercholesterolaemia (heterozygous familial and non-familial hypercholesterolaemia) and combined/mixed dyslipidaemia.
- To reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Paediatric patients (10 – 17 years of age)

LIPITOR is indicated as an adjunct to diet to reduce total-C, LDL-C, and apolipoprotein B levels in boys and postmenarchal girls, > 10 to 17 years of age, with heterozygous familial hypercholesterolaemia if after an adequate trial of diet therapy, the following findings are present:

- LDL-C remains ≥ 4,98 mmol/L (190 mg/dL) or
- LDL-C remains ≥ 4,04 mmol/L (160 mg/dL) and:
  - There is a positive family history of premature cardiovascular disease, or
  - Two or more other cardiovascular disease risk factors are present in the paediatric patient.

Reduction of cardiovascular complications

In patients without clinically evident cardiovascular disease, and with or without dyslipidaemia, but with multiple risk factors for coronary heart disease such as smoking, hypertension, diabetes, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to:

- Reduce the risk of ischaemic cardiovascular and cerebrovascular diseases.

Secondary reduction

- Reduction of cardiovascular events in patients with clinically evident coronary heart disease and

increased cholesterol levels.

Therapy with lipid-lowering medicines should be a component of multiple-risk-factor intervention in individuals at increased risk of atherosclerotic vascular disease due to hypercholesterolaemia. Lipid-altering medicines should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other non-pharmacological measures has been inadequate.

Prior to initiating therapy with LIPITOR, secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemia, obstructive liver disease, other medicine therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG.

4.2 Posology and method of administration

The patient should be placed on a standard cholesterol-lowering diet before receiving LIPITOR and should continue on this diet during treatment with LIPITOR.

Posology

The usual starting dose is 10 mg once a day and should be individualised according to the baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should only be made after an interval of 4 weeks or more. The maximum recommended daily dose is 80 mg once a day.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

The majority of patients are controlled with 10 mg LIPITOR once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous familial hypercholesterolaemia

Patients should be started with LIPITOR 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg LIPITOR once daily.

Homozygous familial hypercholesterolaemia

In a compassionate-use, uncontrolled study of patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of LIPITOR, with a greater than 15 % reduction in LDL-C (18 % – 45 %). The dose of LIPITOR is 10 to 80 mg daily (see section 5.1).

LIPITOR should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients.

Reduction of cardiovascular complications

The dosage range is 10 to 80 mg once daily.

Special populations

Dosage in patients with renal insufficiency

Renal disease has no influence on the plasma concentrations or on the lipid effects of LIPITOR; thus, no adjustment of dose is required (see section 4.4).

Dosage in patients with hepatic dysfunction

In patients with moderate to severe hepatic dysfunction, the therapeutic response to LIPITOR is unaffected but serum levels of the medicine are greatly increased. In patients with chronic alcoholic liver disease, plasma concentrations of LIPITOR are markedly increased. C_{max} and AUC are each 4-fold greater in patients with mild (Child-Pugh class A) liver disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with moderate (Child-Pugh class B) liver disease. Therefore, caution with dosage should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see sections 4.3 and 4.4).

Elderly

Efficacy and safety in patients older than 70 years of age using recommended doses are similar to those seen in the general population.

Paediatric population

Paediatric use should only be carried out by medical practitioners experienced in the treatment of paediatric hyperlipidaemia and patients should be re-evaluated on a regular basis to assess progress.

No clinically significant effect on growth and sexual maturation was observed in a 3-year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight.

Heterozygous familial hypercholesterolaemia in paediatric patients (> 10 – 17 years of age)

Experience in paediatrics is limited to a small number of patients (age 10 – 17 years) with severe dyslipidaemias, such as familial hypercholesterolaemia. Patients should be started with LIPITOR 10 mg daily; the maximum recommended dose is 20 mg/day.

There are limited safety and efficacy data available in children with Heterozygous Familial Hypercholesterolemia between 6 to 10 years of age derived from open-label studies. LIPITOR is not indicated in the treatment of patients below the age of 10 years.

Method of administration

For oral use.

Each daily dose of LIPITOR is given all at once and may be given at any time of day with or without food.

4.3 Contraindications

- Hypersensitivity to atorvastatin or to any of the excipients of LIPITOR (listed in section 6.1).
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal (see section 4.4).
- Patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir.
- Concomitant use with rifampicin, diltiazem and grapefruit juice (see section 4.5).
- Patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) liver impairment.
- Pregnancy and lactation and women of childbearing potential not using adequate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Liver effects

Persistent elevations (> 3 times the upper limit of normal (ULN) which occurred on 2 or more occasions) in serum transaminases occurred in 0,7 % of patients who received LIPITOR in clinical trials. The incidence of these abnormalities was 0,2 %, 0,2 %, 0,6 % and 2,3 % for 10, 20, 40 and 80 mg, respectively.

Liver function tests should be performed before the initiation of treatment with LIPITOR and repeated as clinically indicated. Patients who develop increased serum transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in serum transaminases of greater than 3 times the ULN persist, withdrawal of LIPITOR is recommended (see section 4.3).

If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during

treatment with LIPITOR, promptly interrupt therapy. If an alternate aetiology is not found, do not restart LIPITOR.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent serum transaminase elevations are contraindications to the use of LIPITOR (see section 4.3).

Skeletal muscle effects

Myalgia has been reported in patients treated with LIPITOR (see section 4.8). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values greater than 10 times the upper limit of normal, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur, or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with LIPITOR is increased with concurrent administration of immunosuppressive medicines, including ciclosporin, fibric acid derivatives, nicotinic acid, azole antifungals, erythromycin, clarithromycin, colchicine, letermovir, the hepatitis C protease inhibitors telaprevir, boceprevir, glecaprevir/pibrentasvir, elbasvir/grazoprevir, ledipasvir/sofosbuvir and simeprevir and combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir and cytochrome P450/transporter inhibitors. Medical practitioners considering combined therapy with these medicines should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either medicine. When patients are receiving medicines that increase the plasma concentration of LIPITOR, a lower dose of LIPITOR is recommended (see section 4.5).

The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors (e.g. atorvastatin) and daptomycin (see section 4.5). Consideration should be given to temporarily suspend LIPITOR in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. If co-administration cannot be avoided, CK levels should be measured

2 – 3 times per week and patients should be closely monitored for any signs or symptoms that might represent myopathy.

Muscle-related adverse events have been reported with concomitant administration of LIPITOR and fusidic acid. In patients where the use of systemic fusidic acid is considered essential, LIPITOR treatment should be discontinued throughout the duration of fusidic acid treatment (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. LIPITOR therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed e.g. for the treatment of severe infections, the need for co-administration of LIPITOR and fusidic acid should only be considered on a case-by-case basis and under close medical supervision.

Rhabdomyolysis with or without renal impairment has been reported with the use of LIPITOR. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

LIPITOR therapy should be withdrawn in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

There have been very rare reports of an immune mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment, positive anti-HMG CoA reductase antibody and improvement with immunosuppressive agents.

Protease inhibitors

Co-administration of LIPITOR and protease inhibitors was associated with increased plasma concentrations of LIPITOR.

Haemorrhagic stroke

In a post-hoc analysis of a clinical study, patients without coronary heart disease (CHD) who had a stroke or transient ischaemic attack (TIA) within the preceding 6 months who were initiated on LIPITOR 80 mg revealed a higher incidence of haemorrhagic stroke compared to placebo. Patients with haemorrhagic stroke on entry appeared to be at increased risk for recurrent haemorrhagic stroke.

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). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Endocrine function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including LIPITOR.

Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5,6 to 6,9 mmol/L, BMI > 30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Myasthenia gravis

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). LIPITOR should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Excipients

LIPITOR contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

The risk of myopathy during treatment with LIPITOR is increased with concurrent administration of immunosuppressive medicines, including ciclosporin, fibric acid derivatives, niacin (nicotinic acid) or cytochrome P450 3A4/transporter inhibitors (macrolide antibiotics e.g. erythromycin, and azole antifungals e.g. clotrimazole), colchicine, telaprevir, boceprevir or the combination of tipranavir/ritonavir (see section 4.4 – *Skeletal muscle effects*). CYP3A4 is the primary hepatic isozyme known to be

involved in the biotransformation of atorvastatin. Medical practitioners considering combined therapy with LIPITOR and any of the abovementioned medicines should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either medicine. Therefore, lower starting and maintenance doses of LIPITOR should also be considered when taken concomitantly with the aforementioned medicines.

Inhibitors of cytochrome P450 3A4

LIPITOR is metabolised by cytochrome P450 3A4. Concomitant administration of LIPITOR with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of LIPITOR. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4 (see section 4.4).

Ticagrelor

Co-administration of LIPITOR and ticagrelor increased atorvastatin acid C_{max} by 23 % and AUC by 36 %. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Erythromycin/clarithromycin

Co-administration of LIPITOR and erythromycin or clarithromycin, known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of LIPITOR (see section 4.4 – *Skeletal muscle effects*).

Protease inhibitors

Plasma concentrations of LIPITOR increased with concomitant administration of LIPITOR with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of LIPITOR alone. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of LIPITOR should be avoided. Concomitant administration of LIPITOR 10 mg single dose with tipranavir 500 mg twice daily plus ritonavir 200 mg twice daily for seven days, resulted in a 9,4-fold increase in atorvastatin AUC and 8,6-fold increase in atorvastatin C_{max}. LIPITOR did not result in a change in pharmacokinetics of tipranavir plus ritonavir. Concomitant administration of LIPITOR 20 mg single dose with telaprevir 750 mg every eight hours, for 10 days, resulted in a 7,9-fold increase in atorvastatin AUC and 10,6-fold

increase in atorvastatin C_{max}.

In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPITOR and the lowest dose necessary (not exceeding 10 mg) of LIPITOR should be used. Concomitant administration of LIPITOR 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) resulted in a 5,9-fold increase in atorvastatin AUC. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of LIPITOR should not exceed 20 mg and should be used with caution. Concomitant administration of LIPITOR 40 mg once a day for 4 days with saquinavir 400 mg twice daily plus ritonavir 400 mg twice daily for 15 days resulted in a 3,9-fold increase in atorvastatin AUC and 4,3-fold increase in atorvastatin C_{max}. The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used. Concomitant administration of LIPITOR 10 mg once a day for 4 days with darunavir 300 mg twice daily plus ritonavir 100 mg twice daily for 9 days resulted in a 3,4-fold increase in atorvastatin AUC and 2,3-fold increase in atorvastatin C_{max}. Concomitant administration of LIPITOR 10 mg once a day for 4 days with fosamprenavir 1 400 mg twice a day for 14 days resulted in a 2,3-fold increase in atorvastatin AUC and 4,0-fold increase in atorvastatin C_{max}. LIPITOR resulted in a 1,27-fold decrease in fosamprenavir. Concomitant administration of LIPITOR 10 mg once a day for 4 days with fosamprenavir 700 mg twice a day plus ritonavir 100 mg twice a day for 14 days resulted in a 2,5-fold increase in atorvastatin AUC and 2,8-fold increase in atorvastatin C_{max}. LIPITOR did not result in a change in pharmacokinetics of fosamprenavir 700 mg plus ritonavir.

In patients taking nelfinavir, the dose of LIPITOR should not exceed 40 mg daily. Concomitant administration of LIPITOR 10 mg once a day for 28 days with nelfinavir 1 250 mg twice a day for 14 days resulted in a 74 % increase in atorvastatin AUC and 2,2-fold increase in atorvastatin C_{max}.

Concomitant administration of LIPITOR 40 mg single dose with boceprevir 800 mg three times a day for 7 days resulted in a 2,3-fold increase in atorvastatin AUC and 2,66-fold increase in atorvastatin C_{max} (see section 4.4 – *Skeletal muscle effects*).

Diltiazem hydrochloride

Co-administration of LIPITOR with diltiazem was associated with an increase in AUC of 51 % of

LIPITOR (see section 4.3).

Cimetidine

LIPITOR plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

Itraconazole

Co-administration of LIPITOR 40 mg, single dose and itraconazole 200 mg, once daily, was associated with a 3,3-fold increase in AUC and a 20 % increase in $C_{max.}$

Grapefruit juice

Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of LIPITOR by 2,5 to 3,3-fold and the combination should be avoided (see section 4.3).

Transporter inhibitors

Atorvastatin and atorvastatin metabolites are substrates of the organic anion-transporting polypeptide 1B1 (OATP1B1) transporter (see section 5.2 – *Elimination*). Inhibitors of the OATP1B1 (e.g. ciclosporin) can increase the bioavailability of atorvastatin.

Ciclosporin

Concomitant administration of LIPITOR 10 mg and ciclosporin 5,2 mg/kg/day resulted in an 8,7-fold increase in exposure to atorvastatin. Do not exceed 10 mg LIPITOR daily.

Glecaprevir/pibrentasvir

Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to LIPITOR. Do not exceed 10 mg LIPITOR daily.

Elbasvir/grazoprevir

Elbasvir and grazoprevir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to LIPITOR. Use with caution and lowest dose necessary.

Letermovir

Concomitant administration of LIPITOR 20 mg and letermovir 480 mg daily resulted in an increase in exposure to LIPITOR (ratio of AUC: 3,29). Do not exceed 20 mg LIPITOR daily.

Use of LIPITOR is not recommended in patients taking letermovir co-administered with ciclosporin.

Inducers of cytochrome P450 3A4

Concomitant administration of LIPITOR with inducers of cytochrome P450 3A4 (e.g. efavirenz,

rifampicin, St. John's Wort) can lead to variable reductions in plasma concentrations of LIPITOR. Due to the dual interaction mechanism of rifampicin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of LIPITOR with rifampicin is recommended, as delayed administration of LIPITOR after administration of rifampicin has been associated with a significant reduction in LIPITOR plasma concentrations. The effect of rifampicin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Antacids

Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of LIPITOR approximately 35 %; however, LDL-C reduction was not altered.

Antipyrine

Because LIPITOR does not affect the pharmacokinetics of antipyrine, interactions with other medicines metabolised via the same cytochrome isozymes are not expected.

Colestipol

Plasma concentrations of LIPITOR decreased approximately 25 % when colestipol and LIPITOR were co-administered. However, LDL-C reduction was greater when LIPITOR and colestipol were co-administered than when either medicine was given alone.

Cholestyramine

No data is available.

Digoxin

Co-administration of multiple doses of LIPITOR and digoxin increased steady-state plasma digoxin concentrations by approximately 20 %. Patients taking digoxin should be monitored appropriately.

Azithromycin

Co-administration of LIPITOR (10 mg once daily) and azithromycin (500 mg once daily) did not alter the plasma concentrations of LIPITOR.

Oral contraceptives

Co-administration of LIPITOR and an oral contraceptive increased AUC values of norethindrone and ethinyl estradiol approximately 30 % and 20 %, respectively. These increases should be considered

when selecting an oral contraceptive for a woman taking LIPITOR.

Warfarin

LIPITOR had no clinically significant effect on prothrombin/INR time when administered to patients receiving combined LIPITOR and warfarin therapy for two weeks. Nevertheless, patients receiving LIPITOR should be closely monitored when LIPITOR is combined with warfarin therapy.

Colchicine

Although interaction studies with LIPITOR and colchicine have not been conducted, cases of myopathy have been reported with LIPITOR co-administered with colchicine, and caution should be exercised when prescribing LIPITOR with colchicine.

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. atorvastatin) co-administered with daptomycin. If co-administration cannot be avoided, appropriate clinical monitoring is recommended (see section 4.4).

Amlodipine

LIPITOR pharmacokinetics were not altered by the co-administration of LIPITOR 80 mg and amlodipine 10 mg at steady state.

Fusidic acid

Although interaction studies with LIPITOR and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. The mechanism of this interaction is unknown. If treatment with systemic fusidic acid is necessary, treatment with LIPITOR should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

LIPITOR therapy may be re-introduced seven days after the last dose of fusidic acid.

Other concomitant therapy

In clinical studies, LIPITOR was used concomitantly with antihypertensive medicines and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific medicines have not been conducted.

Table 1: Effect of co-administered medicines on the pharmacokinetics of LIPITOR

Co-administered	**LIPITOR**

medicine and dosing regimen	**Dose (mg)**	**Ratio of AUC[&]**	**Clinical recommendation[#]**
Glecaprevir 400 mg OD/ pibrentasvir 120 mg OD, 7 days	10 mg OD for 7 days	8,3	Co-administration with medicines containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).
Tipranavir 500 mg BID/ ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	9,4	In cases where co-administration with LIPITOR is necessary, do not exceed 10 mg LIPITOR daily. Clinical monitoring of these patients is recommended.
Telaprevir 750 mg q8h, 10 days	20 mg, SD	7,9	
Ciclosporin 5,2 mg/kg/day, stable dose	10 mg OD for 28 days	8,7	
Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	5,9	In cases where co-administration with LIPITOR is necessary, lower maintenance doses of LIPITOR are recommended. At LIPITOR doses exceeding 20 mg, clinical monitoring of these patients is recommended.
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	4,5	

Saquinavir 400 mg BID/ ritonavir (300 mg BID from days 5 – 7, increased to 400 mg BID on day 8), days 4 – 18, 30 min after LIPITOR dosing	40 mg OD for 4 days	3,9	In cases where co-administration with LIPITOR is necessary, lower maintenance doses of LIPITOR are recommended. At LIPITOR doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/ ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	3,4	
Itraconazole 200 mg OD, 4 days	40 mg SD	3,3	
Fosamprenavir 700 mg BID/ ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	2,5	
Fosamprenavir 1 400 mg BID, 14 days	10 mg OD for 4 days	2,3	
Elbasvir 50 mg OD/ grazoprevir 200 mg OD, 13 days	10 mg SD	1,95	The dose of LIPITOR should not exceed a daily dose of 20 mg during co-administration with medicines containing elbasvir or grazoprevir.
Letermovir 480 mg OD, 10 days	20 mg SD	3,29	The dose of LIPITOR should not exceed a daily dose of 20 mg during co-administration with medicines containing letermovir.
Nelfinavir 1 250 mg BID, 14 days	10 mg OD for 28 days	1,74	No specific recommendation.

Grapefruit juice, 240 mL OD*	40 mg, SD	1,37	Concomitant intake of large quantities of grapefruit juice and LIPITOR is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	1,51	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10 mg, SD	1,33	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	1,18	No specific recommendation.
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 2 weeks	1,00	No specific recommendation.
Colestipol 10 g BID, 24 weeks	40 mg OD for 8 weeks	0,74**	No specific recommendation.
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 17 days	10 mg OD for 15 days	0,66	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	0,59	No specific recommendation.
Rifampin 600 mg OD, 7 days (co-administered)	40 mg SD	1,12	If co-administration cannot be avoided, simultaneous co-administration of LIPITOR with rifampicin is recommended, with clinical monitoring.
Rifampicin 600 mg OD, 5 days (doses separated)	40 mg SD	0,20	

Gemfibrozil 600 mg BID, 7 days	40 mg SD	1,35	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40 mg SD	1,03	Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir 800 mg TID, 7 days	40 mg SD	2,3	Lower starting dose and clinical monitoring of these patients is recommended. The dose of LIPITOR should not exceed a daily dose of 20 mg during co-administration with boceprevir.

[&] Represents ratio of treatments (co-administered medicines plus LIPITOR versus LIPITOR alone).

[#] See sections 4.4 and 4.5 for clinical significance.

* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicines metabolised by CYP3A4. Intake of one 240 mL glass of grapefruit juice also resulted in a decreased AUC of 20,4 % for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1,2 L daily for 5 days) increased AUC of atorvastatin 2,5-fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1,3-fold.

** Ratio based on a single sample taken 8 – 16 h post dose.

OD = once daily; SD = single dose; BID = twice daily; TID = three times daily; QID = four times daily.

Table 2: Effect of LIPITOR on the pharmacokinetics of co-administered medicines

LIPITOR and dosing regimen	**Co-administered medicine**		
	Medicine/dose (mg)	**Ratio of AUC[&]**	**Clinical recommendation**
80 mg OD for 10 days	Digoxin 0,25 mg OD, 20 days	1,15	Patients taking digoxin should be monitored appropriately.
40 mg OD for 22 days	Oral contraceptive OD, 2 months		No specific recommendation.

	- norethindrone 1 mg - ethinyl estradiol 35 µg	1,28 1,19	
80 mg OD for 15 days	* Phenazone, 600 mg SD	1,03	No specific recommendation.
10 mg, SD	Tipranavir 500 mg BID/ ritonavir 200 mg BID, 7 days	1,08	No specific recommendation.
10 mg OD for 4 days	Fosamprenavir 1 400 mg BID, 14 days	0,73	No specific recommendation.
10 mg OD for 4 days	Fosamprenavir 700 mg BID/ ritonavir 100 mg BID, 14 days	0,99	No specific recommendation.

[&] Represents ratio of treatments (co-administered medicine plus LIPITOR versus LIPITOR alone).

* Co-administration of multiple doses of LIPITOR and phenazone showed little or no detectable effect in the clearance of phenazone.

OD = once daily; SD = single dose; BID = twice daily.

4.6 Fertility, pregnancy and lactation

LIPITOR is contraindicated in pregnancy, in mothers breastfeeding their infants and in women of childbearing potential not using adequate contraceptive measures (see section 4.3).

Women of childbearing potential

LIPITOR should be administered to women of childbearing age only when such patients are using adequate contraception and have been informed of the potential hazards to the foetus. An interval of one month should be allowed from stopping LIPITOR treatment to conception in the event of planning a pregnancy.

Breastfeeding

LIPITOR is contraindicated while breastfeeding. It is unknown whether LIPITOR is excreted in human milk. Because of the potential for adverse reactions, women taking LIPITOR should not breastfeed their infants (see section 4.3).

4.7 Effects on ability to drive and use machines

LIPITOR has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In placebo-controlled trials, 5,2 % of patients on LIPITOR discontinued treatment due to adverse events compared to 4,0 % of the patients on placebo.

Tabulated summary of adverse reactions

Adverse events have been categorised as follows:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Adverse events in placebo-controlled studies

(% of patients)

System organ class **Adverse event**	**Placebo** **N = 270**	**LIPITOR** **10 mg** **N = 863**	**LIPITOR** **20 mg** **N = 36**	**LIPITOR** **40 mg** **N = 79**	**LIPITOR** **80 mg** **N = 94**
Infections and infestations					
Infection	10,0	10,3	2,8	10,1	7,4
Flu syndrome	1,9	2,2	0,0	2,5	3,2
Immune system disorders					
Allergic reaction	2,6	0,9	2,8	1,3	0,0
Nervous system disorders					
Headache	7,0	5,4	16,7	2,5	6,4
Respiratory, thoracic and mediastinal disorders					
Sinusitis	2,6	2,8	0,0	2,5	6,4
Pharyngitis	1,5	2,5	0,0	1,3	2,1
Gastrointestinal disorders					

Abdominal pain	0,7	2,8	0,0	3,8	2,1
Constipation	1,8	2,1	0,0	2,5	1,1
Diarrhoea	1,5	2,7	0,0	,8	5,3
Dyspepsia	4,1	2,3	2,8	1,3	2,1
Flatulence	3,3	2,1	2,8	1,3	1,1
Skin and subcutaneous tissue disorders					
Rash	0,7	3,9	2,8	3,8	1,1
Musculoskeletal and connective tissue disorders					
Back pain	3,0	2,8	0,0	3,8	1,1
Arthralgia	1,5	2,0	0,0	5,1	0,0
Myalgia	1,1	3,2	5,6	1,3	0,0
General disorders and administration site conditions					
Asthenia	1,9	2,2	0,0	3,8	0,0
Injury, poisoning and procedural complications					
Accidental injury	3,7	4,2	0,0	1,3	3,2

The following additional adverse events have been reported in LIPITOR clinical trials:

System organ class	Frequency	Side effects
Infections and infestations	Common	Nasopharyngitis
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia
Immune system disorders	Common	Allergic reactions (including anaphylaxis)
Metabolism and nutrition disorders	Common	Hyperglycaemia
	Uncommon	Hypoglycaemia, anorexia, weight gain
Psychiatric disorders	Common	Insomnia
	Uncommon	Nightmare

Nervous system disorders	Common	Hypoaesthesia, paraesthesia, dizziness, headache
	Uncommon	Peripheral neuropathy, amnesia, dysgeusia
	Not known	Myasthenia gravis
Eye disorders	Uncommon	Blurred vision
	Not known	Ocular myasthenia
Ear and labyrinth disorders	Uncommon	Tinnitus
Vascular disorders	Rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Pharyngolaryngeal pain, epistaxis
Gastrointestinal disorders	Common	Nausea, diarrhoea, abdominal pain, dyspepsia, constipation, flatulence
	Uncommon	Vomiting, eructation, pancreatitis
Hepatobiliary disorders	Uncommon	Hepatitis
	Rare	Cholestasis, cholestatic jaundice
Skin and subcutaneous tissue disorders	Common	Pruritus, rash
	Uncommon	Alopecia, urticaria
	Rare	Angioedema, bullous rashes, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichenoid drug reaction
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain
	Uncommon	Neck pain, muscle fatigue
	Rare	Myopathy, myositis, rhabdomyolysis, muscle cramps
Reproductive system and breast disorders	Uncommon	Impotence
General disorders and	Common	Asthenia, chest pain

administration site conditions	Uncommon	Malaise, peripheral oedema, fatigue, pyrexia
Investigations	Common	Abnormal liver function test, increased blood creatine kinase
	Uncommon	White blood cells urine positive
Injury, poisoning and procedural complications	Uncommon	Tendon rupture

Paediatric population

Patients treated with LIPITOR had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections.

Post-marketing experience

There have been post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) and immune-mediated necrotizing myopathy associated with use of LIPITOR.

These side effects may be reversible upon discontinuation of treatment.

The following adverse events have been reported with some statins:

- Depression.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no specific treatment for LIPITOR overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Liver function tests should be performed and serum CK levels should be monitored. Due to extensive medicine binding to plasma proteins, haemodialysis is not expected to significantly enhance LIPITOR clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.5 Serum-cholesterol reducers

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol.

The liver is its primary site of action and the principal site of cholesterol synthesis and low-density lipoprotein cholesterol (LDL-C) clearance.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of LDL-C receptors on the cell-surface of liver cells, providing for enhanced uptake and catabolism of LDL-C. Atorvastatin reduces LDL-C production and the number of LDL-C particles. Depending on dose, atorvastatin reduces the number of apolipoprotein B-containing particles in patients with hypercholesterolaemia. Atorvastatin produces a profound and sustained increase in LDL-C receptor activity coupled with a change in the quality of circulating LDL-C particles.

Atorvastatin reduces total cholesterol (total-C), LDL-C, apolipoprotein B in normal volunteers, and in patients with heterozygous familial hypercholesterolaemia, non-familial hypercholesterolaemia, mixed dyslipidaemia, and in some patients with homozygous familial hypercholesterolaemia. It also reduces serum triglycerides (TG) and produces variable increases in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 in non-familial hypercholesterolaemia and mixed dyslipidaemias.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, atorvastatin is rapidly absorbed. The maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. The extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent substance) is approximately 12 % and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30 %. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of absorption by approximately 25 % and 9

%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30 % for C_{max} and AUC) following evening administration compared to morning administration of the medicine. However, LDL-C reduction is the same regardless of the time of medicine administration (see section 4.2).

Distribution

Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is 98 % or more bound to plasma proteins.

Biotransformation

Atorvastatin is extensively metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70 % of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, it does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin (parent substance) in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2 % of a dose of atorvastatin is recovered in urine following oral administration.

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special populations

Elderly

Plasma concentrations of atorvastatin and its active metabolites are higher (approximately 40 % for C_{max} and 30 % for AUC) in healthy elderly subjects (65 years and older) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of atorvastatin.

Gender

Plasma concentrations of atorvastatin and its active metabolites in women differ (approximately 20 % higher for C_{max} and 10 % lower for AUC) from those in men; however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal impairment

Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin. Thus, dose adjustment in patients with renal dysfunction is not necessary (see section 4.2). However, a history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects (see section 4.4).

Haemodialysis

While studies have not been conducted in patients with end-stage renal disease, haemodialysis is not expected to significantly enhance clearance of atorvastatin since the medicine is extensively bound to plasma proteins.

Hepatic impairment

Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh class B) (see section 4.3).

SLCO1B1 polymorphism

Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2,4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Calcium carbonate

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Polysorbate 80

Hydroxypropyl cellulose

Magnesium stearate

Coating

Opadry white

- Hydroxypropyl methylcellulose
- Polyethylene glycol
- Titanium dioxide
- Talc

Simethicone emulsion

- Simethicone
- Stearate emulsifiers
- Thickeners
- Benzoic acid
- Sorbic acid

Candelilla wax (10, 20 and 40 mg tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

LIPITOR 10, 20, 40 and 80: 36 months

6.4 Special precautions for storage

Store at or below 30 °C in a dry place.

6.5 Nature and contents of container

Polyamide-aluminium-PVC/aluminium foil blister packs of 28, 30, 56, 60, 84, 90, 100 and 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

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Manufacturer: Viatris Pharmaceuticals LLC, Vega Baja, Puerto Rico

8. REGISTRATION NUMBERS

LIPITOR 10: 31/7.5/0357

LIPITOR 20: 31/7.5/0358

LIPITOR 40: 31/7.5/0359

LIPITOR 80: 37/7.5/0210

9. DATE OF FIRST AUTHORISATION

LIPITOR 10: 23 July 1997

LIPITOR 20: 23 July 1997

LIPITOR 40: 23 July 1997

LIPITOR 80: 11 February 2005

10. DATE OF REVISION OF THE TEXT

22 August 2025

BOTSWANA: S2

LIPITOR 10 – Reg. No. BOT0400688

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LIPITOR 40 – Reg. No. BOT0400690

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LIPITOR 10 – Reg. No. 04/7.5/1224

LIPITOR 20 – Reg. No. 04/7.5/1225

LIPITOR 40 – Reg. No. 04/7.5/1226

LIPITOR 80 – Reg. No. 07/7.5/0122

ZAMBIA: POM

LIPITOR 10 – Reg. No. 120/005

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