SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

ASPAVOR® 10 Tablet

ASPAVOR® 20 Tablet

ASPAVOR® 40 Tablet

ASPAVOR® 80 Tablet

COMPOSITION:

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

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

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

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

ASPAVOR tablets contain the following inactive ingredients: Calcium carbonate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, polysorbate 80, hydroxypropyl cellulose and magnesium stearate.

The coating of ASPAVOR tablets contains Opadry white (consisting of hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and talc) and simethicone emulsion (consisting of simethicone, stearate emulsifiers, thickeners, benzoic acid and sorbic acid). The 10, 20, and 40 mg tablets also contain candelilla wax.

PHARMACOLOGICAL CLASSIFICATION:

A 7.5 Serum-cholesterol reducers

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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 an 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.

Pharmacokinetic properties:

Absorption:

Following oral administration, maximum plasma concentrations occur within 1 to 2 hours. 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 DOSAGE AND DIRECTIONS FOR USE).

Distribution:

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

Metabolism:

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.

Excretion:

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, it does not appear to undergo 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.

Special populations:

Elderly:

Plasma concentrations of atorvastatin 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 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 insufficiency:

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 DOSAGE AND DIRECTIONS FOR USE). 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 WARNINGS AND SPECIAL PRECAUTIONS).

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 insufficiency:

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

INDICATIONS:

Hypercholesterolaemia:

ASPAVOR is indicated:

1. As an adjunct to diet for reduction of elevated total-cholesterol, LDL-cholesterol, apolipoprotein-B, and triglyceride levels and to moderately increase HDL-cholesterol in patients with primary hypercholesterolaemia (heterozygous familial and non-familial hypercholesterolaemia) and combined/mixed dyslipidaemia;
2. To reduce total-C and LDL-C in 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):

ASPAVOR is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo 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:

a) LDL-C remains ≥ 4,98 mmol/L (190 mg/dL) or

b) 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 CVD risk factors are present in the paediatric patient

Prevention 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, ASPAVOR is indicated to:

- Reduce the risk of ischaemic cardiovascular and cerebrovascular diseases.

Secondary prevention:

Prevention of cardiovascular events in patients with clinically evident coronary heart disease and increased cholesterol levels.

Therapy with lipid-lowering agents should be a component of multiple-risk-factor intervention in individuals at increased risk of atherosclerotic vascular disease due to hypercholesterolaemia. Lipid-altering agents 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 ASPAVOR, 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.

CONTRAINDICATIONS:

Hypersensitivity to atorvastatin or to any of the components of ASPAVOR.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal (see WARNINGS AND SPECIAL PRECAUTIONS).

Concomitant use with rifampicin, diltiazem and grapefruit juice (see INTERACTIONS).

Patients with Child-Pugh B and C (liver cirrhosis).

Pregnancy and lactation (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS:

Liver effects:

Persistent elevations (> 3 times the upper limit of normal (ULN) occurring on 2 or more occasions) in serum transaminases occurred in 0,7 % of patients who received ASPAVOR 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.

It is recommended that liver function tests be performed before the initiation of treatment with ASPAVOR and repeated as clinically indicated. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with ASPAVOR, promptly interrupt therapy. If an alternate aetiology is not found, do not restart ASPAVOR.

ASPAVOR 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 transaminase elevations

are contraindications to the use of ASPAVOR (see CONTRAINDICATIONS).

Skeletal muscle:

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

Myalgia has been reported in patients treated with ASPAVOR (see SIDE EFFECTS). 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. ASPAVOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with ASPAVOR is increased with concurrent administration of immunosuppressive medicines, including ciclosporin, fibric acid derivatives, nicotinic acid, azole antifungals or erythromycin, colchicine, the hepatitis C protease inhibitor telaprevir, boceprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, atazanavir plus ritonavir and fosamprenavir plus ritonavir and cytochrome P450 inhibitors. Medical practitioners considering combined therapy with ASPAVOR and fibric acid derivatives, erythromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, atazanavir plus ritonavir, immunosuppressive medicines, azole antifungals, or lipid-modifying doses of niacin 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. Muscle-related adverse events have been reported with concomitant ASPAVOR and fusidic acid. Temporary suspension of ASPAVOR may be appropriate during fusidic acid therapy (see INTERACTIONS).

ASPAVOR 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).

Protease inhibitors:

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

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 atorvastatin 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.

Endocrine function:

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

Lactose intolerance:

ASPAVOR tablets contain lactose. ASPAVOR should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

INTERACTIONS:

The risk of myopathy during treatment with ASPAVOR is increased with concurrent administration of immunosuppressive medicines, including ciclosporin, fibric acid derivatives, niacin (nicotinic acid) or cytochrome P450 3A4 inhibitors (macrolide antibiotics e.g. erythromycin, and azole antifungals e.g. clotrimazole) (see WARNINGS AND SPECIAL PRECAUTIONS – Skeletal muscle).

Inhibitors of cytochrome P450 3A4:

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

Transporter inhibitors:

Inhibitors of the OATP1B1 (e.g. ciclosporin) can increase the bioavailability of atorvastatin. Concomitant administration of ASPAVOR 10 mg and ciclosporin 5,2 mg/kg/day resulted in an 8,7-fold increase in exposure to atorvastatin.

Erythromycin/clarithromycin:

In healthy individuals, plasma concentrations of ASPAVOR increased approximately 40 % with co-administration of ASPAVOR and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS AND SPECIAL PRECAUTIONS – Skeletal muscle).

Combination of protease inhibitors:

Plasma concentrations of atorvastatin increased with concomitant administration of ASPAVOR with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of ASPAVOR alone. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of ASPAVOR should be avoided. Concomitant administration of ASPAVOR 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}. ASPAVOR did not result in a change in pharmacokinetics of tipranavir plus ritonavir. Concomitant administration of ASPAVOR 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 ASPAVOR and the lowest dose necessary should be used. Concomitant administration of ASPAVOR 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, atazanavir plus ritonavir, the dose of ASPAVOR should not exceed 20 mg and should be used with caution. Concomitant administration of ASPAVOR 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 ASPAVOR 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 ASPAVOR 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}. ASPAVOR resulted in a 1,27-fold decrease in fosamprenavir. Concomitant administration of ASPAVOR 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}. ASPAVOR did not result in a change in pharmacokinetics of fosamprenavir plus ritonavir.

In patients taking nelfinavir, the dose of ASPAVOR should not exceed 40 mg daily. Concomitant administration of ASPAVOR 10 mg once a day for 28 days with nelfinavir 1250 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 ASPAVOR 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 WARNINGS AND SPECIAL PRECAUTIONS – Skeletal muscle).

Diltiazem hydrochloride:

Co-administration of ASPAVOR with diltiazem was associated with an increase in AUC of 51 % of ASPAVOR (see CONTRAINDICATIONS).

Cimetidine:

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

Itraconazole:

Co-administration of ASPAVOR 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 CYP 3A4 and can increase plasma concentrations of ASPAVOR by 2,5 to 3,3-fold and the combination should be avoided (see CONTRAINDICATIONS).

Inducers of cytochrome P450 3A4:

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

rifampicin) can lead to variable reductions in plasma concentrations of ASPAVOR. Due to the dual interaction mechanism of rifampicin, simultaneous co-administration of ASPAVOR with rifampicin is not recommended, as delayed administration of ASPAVOR after administration of rifampicin has been associated with a significant reduction in ASPAVOR plasma concentrations.

Antacids:

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

Antipyrine:

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

Colestipol:

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

Cholestyramine:

No data are available.

Digoxin:

Co-administration of multiple doses of ASPAVOR and digoxin increased steady-state plasma digoxin concentrations by approximately 20 %. Patients taking digoxin should be monitored appropriately (see WARNINGS AND SPECIAL PRECAUTIONS).

Azithromycin:

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

Oral contraceptives:

Co-administration of ASPAVOR 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 ASPAVOR.

Warfarin:

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

Colchicine:

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

Amlodipine:

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

Fusidic acid:

Although interaction studies with ASPAVOR and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of ASPAVOR treatment may be appropriate.

Other concomitant therapy:

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

PREGNANCY AND LACTATION:

ASPAVOR is contraindicated in pregnancy, in mothers breastfeeding their infants and in women of childbearing potential not using adequate contraceptive measures. ASPAVOR 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 ASPAVOR treatment to conception in the event of planning a pregnancy.

DOSAGE AND DIRECTIONS FOR USE:

The patient should be placed on a standard cholesterol-lowering diet before receiving ASPAVOR and

should continue on this diet during treatment with ASPAVOR.

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 will depend on the indication (see below). Doses may be given at any time of day with or without food.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia:

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

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 ASPAVOR 10 mg daily, the maximum recommended dose is 20 mg/day.

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 ASPAVOR, with a greater than 15 % reduction in LDL-C (18 % – 45 %).

Prevention of cardiovascular complications:

The dosage range is 10 to 80 mg once daily.

Dosage in patients with renal insufficiency:

Renal disease has no influence on the plasma concentrations or on lipid effects of ASPAVOR; thus, no adjustment of dose is required (see WARNINGS AND SPECIAL PRECAUTIONS).

Dosage in patients with hepatic dysfunction:

In patients with moderate to severe hepatic dysfunction, the therapeutic response to ASPAVOR is unaffected but serum levels of the medicine are greatly increased. In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Child-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Child-Pugh B 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 CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

SIDE EFFECTS:

Adverse events have been categorised as follows:

Very common: ≥ 1/10 (≥ 10 %), Common: ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %), Uncommon: ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %), Rare: ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %), Very rare: < 1/10 000 (< 0,01 %).

Adverse events in placebo-controlled studies

(% of patients)

System Organ Class Adverse event	**Placebo** **N = 270**	**Atorvastatin 10 mg** **N = 863**	**Atorvastatin 20 mg** **N = 36**	**Atorvastatin 40 mg** **N = 79**	**Atorvastatin 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
Nervous system disorders					
Headache	7,0	5,4	16,7	2,5	6,4
Injury and poisoning					
Accidental injury	3,7	4,2	0,0	1,3	3,2
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	3,8	5,3
Dyspepsia	4,1	2,3	2,8	1,3	2,1
Flatulence	3,3	2,1	2,8	1,3	1,1

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
Immune system disorders					
Allergic reaction	2,6	0,9	2,8	1,3	0,0
General disorders and administration site conditions					
Asthenia	1,9	2,2	0,0	3,8	0,0
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
Skin and subcutaneous tissue disorders					
Rash	0.7	3,9	2,8	3,8	1,1

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

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia
Ear and labyrinth disorders	Uncommon	Tinnitus
Gastrointestinal disorders	Common	Nausea, diarrhoea, abdominal pain, dyspepsia, constipation, flatulence

	Uncommon	Vomiting
	Rare	Pancreatitis
General disorders and administration site conditions	Common	Asthenia, chest pain
	Uncommon	Malaise
	Rare	Peripheral oedema
	Very rare	Fatigue
Hepatobiliary disorders	Rare	Hepatitis, cholestatic jaundice
Immune system disorders	Common	Allergic reaction (including anaphylaxis)
Injury and poisoning	Uncommon	Tendon rupture
Metabolism and nutrition disorders	Uncommon	Hypoglycaemia, hyperglycaemia, anorexia, weight gain
Nervous system disorders	Common	Hypoaesthesia, paraesthesia, dizziness, headache
	Uncommon	Peripheral neuropathy, amnesia, dysgeusia
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia, back pain
	Rare	Myositis, muscle cramps
	Very rare	Rhabdomyolysis, myopathy
Psychiatric disorders	Common	Insomnia
Reproductive system and breast disorders	Uncommon	Impotence
Skin and subcutaneous tissue disorders	Common	Pruritus, rash
	Uncommon	Alopecia, urticaria
	Rare	Bullous rashes
	Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Paediatric patients:

Patients treated with atorvastatin 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 reports:

There have been post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally not serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks). Immune mediated necrotising myopathy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no specific treatment for ASPAVOR overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive medicine binding to plasma proteins, haemodialysis is not expected to significantly enhance ASPAVOR clearance.

IDENTIFICATION:

ASPAVOR 10: A white, elliptical, film-coated tablet, debossed with '10' on one side and 'PD 155' on the other.

ASPAVOR 20: A white, elliptical, film-coated tablet, debossed with '20' on one side and 'PD 156' on the other.

ASPAVOR 40: A white, elliptical, film-coated tablet, debossed with '40' on one side and 'PD 157' on the other.

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

PRESENTATION:

Silver coloured polyamide/aluminium foil/PVC blister (foil blister) that are packed in an outer cardboard carton with a package insert. ASPAVOR tablets are available in pack sizes of 28, 30, 56, 60, 84, 90, 100 or 500 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C in a dry place. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ASPAVOR 10: A39/7.5/0017

ASPAVOR 20: A39/7.5/0018

ASPAVOR 40: A39/7.5/0019

ASPAVOR 80: 43/7.5/0837

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

22 April 2016

BOTSWANA: S2

ASPAVOR 10 – Reg. No. BOT1101986

ASPAVOR 20 – Reg. No. BOT1101987

ASPAVOR 40 – Reg. No. BOT1101988

NAMIBIA: NS2

ASPAVOR 10 – Reg. No. 07/7.5/0125

ASPAVOR 20 – Reg. No. 07/7.5/0124

ASPAVOR 40 – Reg. No. 07/7.5/0123

ZAMBIA: POM

ASPAVOR 10 – Reg. No. 357/001

ASPAVOR 20 – Reg. No. 357/002

ASPAVOR 40 – Reg. No. 357/003

ZIMBABWE: PP

ASPAVOR 10 – Reg. No. 2012/12.8/4722

ASPAVOR 20 – Reg. No. 2012/12.8/4723

ASPAVOR 40 – Reg. No. 2012/12.8/4724