SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

VASTOR 10 mg (film-coated tablets)

VASTOR 20 mg (film-coated tablets)

VASTOR 40 mg (film-coated tablets)

VASTOR 80 mg (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VASTOR 10 mg: Each film-coated tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

Contains sugar: Lactose anhydrous 42,5 mg.

VASTOR 20 mg: Each film-coated tablet contains atorvastatin calcium equivalent to 20 mg atorvastatin.

Contains sugar: Lactose anhydrous 85 mg.

VASTOR 40 mg: Each film-coated tablet contains atorvastatin calcium equivalent to 40 mg atorvastatin.

Contains sugar: Lactose anhydrous 170 mg.

VASTOR 80 mg: Each film-coated tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin.

Contains sugar: Lactose anhydrous 340 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

VASTOR 10 mg: White, oval, biconvex, film-coated tablet, plain on one side and debossed ‘10’ on the other side.

VASTOR 20 mg: White, oval biconvex, film-coated tablet with break line on one side and debossed ‘20’ on the other side.

VASTOR 40 mg: White, oval, biconvex film-coated tablet with break line on one side and debossed ‘40’ on the other side.

VASTOR 80 mg: White, oval, biconvex, film-coated table with break line on one side and debossed ‘80’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VASTOR is indicated as an adjunct to diet for reduction of elevated total-cholesterol, LDL-cholesterol, apolipoprotein-B, and triglyceride levels in patients with primary hypercholesterolaemia; mixed dyslipidaemia; and heterozygous familial hypercholesterolaemia.

VASTOR is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL aphaeresis) or if such treatments are unavailable.

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 VASTOR, secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, 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

Posology

- The patient should be placed on a standard cholesterol-lowering diet before receiving VASTOR and should continue on this diet during treatment with VASTOR.
- The usual starting dose is 10 mg once a day.
- Doses 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 dose is 40 mg once a day.
- Doses may be given at any time of day with or without food.

Primary non-familial hypercholesterolaemia and combined (mixed) hyperlipidaemia

- The majority of patients are controlled with 10 mg VASTOR 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

Patients should be started with VASTOR 10 mg daily.

Doses should be individualised and adjusted every 4 weeks to 40 mg daily.

Thereafter, a bile acid sequestrant (e.g. colestipol) may be combined with 40 mg VASTOR.

Homozygous familial hypercholesterolaemia

Adults

In a compassionate-use, uncontrolled study of 29 patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of VASTOR, with a mean reduction in LDL-C of 20 % (range 7 – 53 %), although in some patients an increase of LDL-C occurred.

Special populations

Dosage in patients with renal insufficiency

Renal disease has no influence on the plasma concentrations or lipid effects of VASTOR; therefore, no dosage adjustment is necessary (see section 4.4).

Dosage in patients with hepatic dysfunction

- In patients with moderate to severe hepatic dysfunction, the therapeutic response to VASTOR 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. Caution with dosage should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see section 4.3 and 4.4).

Paediatric population

Treatment experience in the homozygous familial hypercholesterolaemia paediatric population with VASTOR is limited.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to atorvastatin or other statins or to any other component of the excipients of VASTOR (listed in section 6.1).
- Concomitant use of ciclosporin and VASTOR (see section 4.5).
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal (see section 4.4 and 4.8).
- Pregnancy and lactation (see section 4.6).
- Patients with myopathy (see section 4.4).
- Patients with Child-Pugh B and C liver cirrhosis.
- Concomitant use with rifampicin, diltiazem and grapefruit juice (see section 4.5).
- Patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

4.4 Special warnings and precautions for use

Liver effects

VASTOR 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 transaminases elevations are contraindications to the use of VASTOR (see section 4.3).

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 atorvastatin in clinical trials.

It is recommended that liver function tests be performed before the initiation of treatment, following each dosage increase, and periodically thereafter. Liver enzyme changes mostly commence in the first 4 months of treatment with atorvastatin. Patients who develop increased transaminases levels should be monitored until the abnormalities resolve.

Should an increase in ALT or AST of > 3 times ULN persist, withdrawal of VASTOR is recommended (see section 4.3).

Skeletal muscle

Rhabdomyolysis with or without renal impairment has been reported with the use of HMG-CoA

reductase inhibitors, such as VASTOR. A history of renal impairment, hypothyroidism, history of hereditary muscular disorders, history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate, alcohol abuse, age > 70 years, concomitant use of fibrates and situations where an increase in plasma levels may occur. These patients merit closer monitoring for skeletal muscle adverse effects. Myalgia has been reported in patients treated with VASTOR (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. VASTOR therapy should be discontinued if markedly elevated CPK levels occur, or myopathy is diagnosed or suspected (see section 4.3).

Concomitant treatment with other medicines

The risk of myopathy during treatment with VASTOR is increased with concurrent administration of immunosuppressive medicines, including ciclosporin [which is contraindicated (see section 4.3)], fibric acid derivatives, nicotinic acid, azole antifungals or macrolides e.g. erythromycin or 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, and fosamprenavir plus ritonavir and cytochrome P450 inhibitors. Medical practitioners considering combined therapy with VASTOR and fibric acid derivatives, erythromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir 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 VASTOR and fusidic acid.

Risk of rhabdomyolysis is increased when VASTOR is administered concomitantly with certain medicines that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins [e.g. ciclosporin (which is contraindicated (see section 4.3)], telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole,

posaconazole, letermovir and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc).

Muscle-related adverse events have been reported with concomitant use of VASTOR and fusidic acid. VASTOR must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, VASTOR treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and VASTOR in combination (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. VASTOR therapy may be re-introduced seven days after the last dose of fusidic acid.

VASTOR 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. VASTOR should be used with caution in patients who have severe renal impairment.

Protease inhibitors

Co-administration of VASTOR and protease inhibitors was associated with increased plasma concentrations of VASTOR (see section 4.5).

Haemorrhagic stroke

Patients without cardiac heart failure (CHF) who had a stroke or transient ischaemic attack (TIA) within the preceding months who were initiated on VASTOR 80 mg revealed a higher incidence of haemorrhagic stroke compared to placebo.

Endocrine function

Increases in glycosylated haemoglobin (HbA1c), fasting serum glucose levels and worsening of glycaemic control have been reported with the use of atorvastatin, such as VASTOR. VASTOR should therefore be used with care in patients with Type 2 diabetes.

Interstitial lung disease

Interstitial lung disease has been reported with some statins such as VASTOR, especially with long term therapy (see section 4.8). Symptoms 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, VASTOR therapy should be discontinued.

Myasthenia gravis and ocular myasthenia

There is a risk of myasthenia gravis and ocular myasthenia with the use of statin-containing medicines, such as VASTOR.

Lactose warning

VASTOR contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients who are lactose intolerant or have rare hereditary problems of galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption should not take VASTOR.

4.5 Interaction with other medicines and other forms of interaction

Effect of co-administered medicines on VASTOR (see Table 1)

The risk of myopathy during treatment with VASTOR is increased with concomitant administration of immunosuppressive medicines e.g. ciclosporin [which is contraindicated (see section 4.3)], fibric acid derivatives (e.g. gemfibrozil), macrolide antibiotics (e.g. erythromycin), azole antifungals (e.g. clotrimazole), or niacin (nicotinic acid) (see section 4.4).

Transporter inhibitors

Inhibitors of the OATP1B1 e.g. ciclosporin [which is contraindicated (see section 4.3)] and letermovir, can increase the plasma concentration of atorvastatin as contained in VASTOR (see section 4.4) (see Table 1).

Inhibitors of cytochrome P450 3A4

VASTOR is metabolised by cytochrome P450 3A4. Concomitant administration of VASTOR with potent inhibitors of cytochrome P450 3A4 (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole), some antivirals used in the treatment of HCV (e.g. elbasvir/grazoprevir) and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc should be avoided if possible (see Table 1).

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may lead to increased plasma concentrations of VASTOR.

Examples of cytochrome P450 3A4 inhibitors are:

Erythromycin

In healthy subjects, plasma concentrations of VASTOR increased approximately 40 % with concurrent administration of VASTOR and erythromycin (see section 4.4, Skeletal muscle).

Azole antifungals

Co-administration of atorvastatin with azole antifungals increase the plasma concentration of atorvastatin and may increase the adverse effects of VASTOR (see section 4.4). For example, co-administration of atorvastatin (20 – 40 mg) and itraconazole (200 mg) was associated with an increase of atorvastatin AUC.

Protease inhibitors

Co-administration of protease inhibitors and atorvastatin is associated with increased plasma concentrations of atorvastatin as contained in VASTOR. This increase in systemic exposure to atorvastatin may lead to increased incidence of adverse effects (see section 4.4).

Combination of protease inhibitors

Plasma concentrations of atorvastatin as contained in VASTOR increased with concomitant administration of VASTOR with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir (see Table 1).

Fusidic acid

Severe muscle problems such as rhabdomyolysis have been reported with the concomitant use of fusidic acid and atorvastatin. Patients on fusidic acid and VASTOR should be closely monitored and temporary suspension of VASTOR may be appropriate (see section 4.4, Skeletal muscle).

Diltiazem HCl

Co-administration of atorvastatin with diltiazem was associated with an increase in the AUC of 51 % of atorvastatin, as contained in VASTOR. Therefore, the combination is contraindicated (see section 4.3).

Grapefruit juice

Co-administration of grapefruit juice and atorvastatin may increase the concentration of atorvastatin (contained in VASTOR) 2,5 – 3,3-fold. Therefore, the combination is contraindicated (see section 4.3).

Cimetidine

Plasma concentrations of atorvastatin and LDL-C reduction were not altered by concomitant

administration of cimetidine.

Inducers of cytochrome P450

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 such as efavirenz and rifampicin can lead to variable reductions in plasma concentrations of atorvastatin as contained in VASTOR. Due to the dual mechanism of rifampicin, simultaneous co-administration of VASTOR with rifampicin is not recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations (see section 4.3).

Antacid

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

Antipyrine

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

Ezetimibe

Muscle related events may be increased with concomitant use of ezetimibe and VASTOR.

Colestipol

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

Cholestyramine

Data is not available.

Azithromycin

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

Effect of VASTOR on co-administered medicines (Table 2)

Digoxin

Concomitant administration of multiple doses of VASTOR and digoxin increased steady-state plasma

digoxin concentrations by approximately 20 %. Patients taking digoxin should be monitored.

Oral contraceptives

Concomitant administration of VASTOR and an oral contraceptive increased AUC values of norethindrone and ethinyl oestradiol approximately 30 % and 20 %, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin

VASTOR had no clinically significant effect on prothrombin time when administered to patients who received combined VASTOR and warfarin therapy for two weeks. Patients receiving VASTOR should, however, be closely monitored when VASTOR is combined with warfarin therapy.

Colchicine

Myopathy has been reported with VASTOR co-administered with colchicine, and caution should be exercised when prescribing VASTOR with colchicine.

Other concomitant therapy

VASTOR was used concomitantly with antihypertensive medicines and oestrogen 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 VASTOR

Co-administered medicine and dosing regimen	**Atorvastatin as contained in VASTOR**		
	Dose (mg)	**Ratio of AUC[&]**	**Recommendation[#]**
Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7 days	10 mg OD for 7 days	8.3	Co-administration with products 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 atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended.
Telaprevir 750 mg q8h, 10	20 mg,	7.9	

days	SD		**Contraindicated** (see section 4.3).
Ciclosporin		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 atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin 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 to 7, increased to 400 mg BID on day 8), days 4 to 18, 30 min after atorvastatin dosing	40 mg OD for 4 days	3.9	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin 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 1400 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 atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing elbasvir or grazoprevir.

Letermovir 480 mg OD, 10 days	20 mg SD	3.29	The dose of atorvastatin should not exceed a daily dose of 20 mg during co administration with products containing letermovir.
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	1.74	No specific recommendation.
Grapefruit Juice		1.37	Concomitant intake of grapefruit juice and atorvastatin is **contraindicated** (see section 4.3).
Diltiazem		1.51	Co-administration with VASTOR is **contraindicated** (see section 4.3).
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.

Rifampicin		1.12 0.20	Co-administration with VASTOR is contraindicated (see section 4.3).
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 atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir.

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

[#] See sections 4.4 and 4.5.

** 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 VASTOR on co-administered medicines

VASTOR and dosing regimen	**Co-administered medicine**		
	Medicine/Dose (mg)	**Ratio of AUC[&]**	**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 - norethindrone 1 mg - ethinyl estradiol 35 µg	1.28	No specific recommendation.
80 mg OD for 15 days	*Phenazone, 600 mg SD	1.19	No specific recommendation.
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7	1.03	No specific recommendation.

	days		
10 mg, OD for 4 days	Fosamprenavir 1400 mg BID, 14 days	1.08	No specific recommendation.
10 mg OD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	0.73	No specific recommendation.

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

* Co-administration of multiple doses of atorvastatin 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

Women of childbearing potential

VASTOR is contraindicated in women of childbearing potential not using adequate contraceptive measures. An interval of one month should be allowed from stopping VASTOR treatment to conception in the event of planning a pregnancy.

Pregnancy

VASTOR is contraindicated in pregnancy.

Breastfeeding

VASTOR is contraindicated in breastfeeding.

4.7 Effects on ability to drive and use machines

VASTOR may cause dizziness and confusion. Patients should be instructed that if they experience these symptoms, they should avoid potentially hazardous tasks, such as driving or operating machinery.

4.8 Undesirable effects

Side effects have been reported:

Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Frequent	**Less frequent**	**Frequency not known**
Blood and lymphatic system disorders		Anaemia, neutropenia, thrombocytopenia	
Immune system disorders	Allergic reactions (including anaphylaxis)	Angioedema	
Metabolism and nutrition disorders	Hyperglycaemia (increased serum glucose levels)	Weight gain, hypoglycaemia, anorexia	
Psychiatric disorders		Nightmares, insomnia	
Nervous system disorders	Headache, dizziness, paraesthesia, hypoaesthesia	Peripheral neuropathy, amnesia, dysgeusia, cognitive impairment such as memory loss, forgetfulness, memory impairment and confusion	Myasthenia gravis
Eye disorders		Vision blurred, visual disturbance	Ocular myasthenia
Ear and labyrinth disorders		Tinnitus, hearing loss	
Vascular disorders		Peripheral oedema	
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain, epistaxis	Sinusitis, pharyngitis	

Gastrointestinal disorders	Nausea, diarrhoea, abdominal pain, dyspepsia, constipation, flatulence	Vomiting, pancreatitis, eructation	
Hepatobiliary disorders		Hepatitis, cholestatic jaundice, hepatic failure	
Skin and subcutaneous tissue disorders	Pruritus, skin rashes	Alopecia, bullous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, urticaria, angioneurotic oedema	
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia, back pain, pain in extremity, muscle spasms, joint swelling	Myopathy, myositis, rhabdomyolysis, muscle cramps, neck pain, muscle rupture, tendinopathy, sometimes complicated by rupture, lupus-like syndrome	Immune mediated necrotizing myopathy (see section 4.4)
Reproductive system and breast disorders		Impotence, gynaecomastia	
General disorders and administration site conditions:	Asthenia, chest pain, flu syndrome, infection	Malaise, fatigue, peripheral oedema, pyrexia	

Investigations	Abnormal liver function test, increased blood creatine kinase	Positive white blood cells urine	
Injury, poisoning and procedural complications		Accidental injury, tendon rupture	

Post-marketing reports

There have been reports of cognitive impairment (such as memory loss, forgetfulness, amnesia, memory impairment and confusion) associated with atorvastatin use, such as VASTOR. These reported symptoms were generally not serious and reversible upon discontinuation with variable times to symptom onset (between a day to years) and symptom resolution with a median of 3 weeks.

The following adverse events have been reported with some statins such as VASTOR:

- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long-term therapy (see section 4.4).
- Diabetes mellitus.

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 asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

There is no specific treatment for VASTOR overdosage.

In the event of overdosage, the patient should be treated symptomatically, and supportive measures instituted as required.

Due to extensive binding to plasma proteins, haemodialysis is not expected to significantly enhance

atorvastatin clearance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA-reductase inhibitors, ATC code: C10AA05

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.

Atorvastatin lowers plasma cholesterol and lipoprotein levels in animal models 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. It reduces LDL-C production and the number of LDL-C particles.

5.2 Pharmacokinetic properties

Absorption

After oral administration maximum plasma concentrations occur within 1 – 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 medicine 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 medicine administration compared to morning administration. 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 litres. It is 98 % or more bound to plasma proteins.

Metabolism

It 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

It 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 are higher 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.

Paediatric

No pharmacokinetic data in the paediatric population is available.

Renal insufficiency

Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin.

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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal anhydrous silica (Aerosil 200)

Croscarmellose sodium

Hydroxypropyl cellulose

L-arginine

Lactose anhydrous

Magnesium stearate

Microcrystalline cellulose

Sodium carbonate anhydrous

Film-coat

Opadry AMB white OY-B-28920

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a cool and dry place at or below 25 °C.

The HDPE bottles must be kept tightly closed.

Do not remove blisters from carton until required for use.

6.5 Nature and contents of container

HDPE bottle pack (without stabilox)

High-density polyethylene (HDPE) bottle pack comprises of white opaque HDPE bottle provided along with a polypropylene (PP) screw cap. The HDPE bottle is placed in a carton (excl. tender).

Pack sizes: 28’s, 30’s, 90’s and 500’s.

HDPE bottle pack (with activated carbon)

High-density polyethylene (HDPE) bottle pack comprises of white opaque HDPE bottle with desiccant

(activated Carbon Minipax) sachet provided with a polypropylene (PP) screw cap. The HDPE bottle is placed in a carton (exc. tender).

Pack sizes: 28's, 30's 90's and 500's.

Cold form blister pack

Cold form blister pack (marketable pack) comprises of cold form laminate on one side [aluminium foil laminated to oriented polyamide on one side and laminated to PVC on other side (i.e. OPA/Al/PVC)] and hard tempered aluminium foil coated with heat seal lacquer on the other side. The blisters are placed in a carton.

7 or 10 tablets per blister strip packed as 28's or 30's.

PVC/Aclar blister pack

PVC/Aclar blister pack comprises of clear, transparent, PVC laminated with Aclar on one side and hard tempered aluminium foil coated with VMCH heat seal lacquer on the other side. The blisters are placed in a carton.

7, 10 or 15 tablets per blister strip packed as 28's or 30's.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

8 REGISTRATION NUMBERS

VASTOR 10 mg: 45/7.5/0527

VASTOR 20 mg: 45/7.5/0528

VASTOR 40 mg: 45/7.5/0529

VASTOR 80 mg: 45/7.5/0530

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

20 June 2013

10 DATE OF REVISION OF TEXT

23 August 2024