PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

LESTAVOR® 10 film-coated tablets

LESTAVOR® 20 film-coated tablets

LESTAVOR® 40 film-coated tablets

LESTAVOR® 80 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

LESTAVOR contain sugar (as lactose monohydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

LESTAVOR 10: White oval biconvex film-coated tablets, approximately 10,1 x 5,6 mm and 3,7 mm in thickness.

LESTAVOR 20: White oval biconvex film-coated tablets with a non-functional breakline on one side, approximately 12,7 x 6,7 mm and 4,6 mm in thickness.

LESTAVOR 40: White oblong biconvex film-coated tablets, approximately 19,4 x 7,8 mm and 4,7 mm in thickness.

LESTAVOR 80: White oblong biconvex film-coated tablets with a non-functional breakline on one side, approximately 22,8 x 10,9 mm and 5,7 mm in thickness.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LESTAVOR is indicated, in combination with diet, to decrease elevated total cholesterol, LDL-cholesterol, apolipoprotein-B and triglyceride levels in patients with:

- primary hypercholesterolaemia,
- heterozygous familial hypercholesterolaemia, and
- mixed dyslipidaemia.

LESTAVOR 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 apheresis), of if such treatments are not available.

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.

Secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, nephrotic syndrome, hypothyroidism, obstructive liver disease, dysproteinaemias,

alcoholism and therapy with other medicines) should be excluded prior to initiating therapy with LESTAVOR, and a lipid profile performed to measure total-C, LDL-C, HDL-C and triglycerides.

4.2 Posology and method of administration

The patient must follow a cholesterol-lowering diet before initiation of, and while on LESTAVOR therapy.

LESTAVOR can be taken at any time of the day with meals or on an empty stomach.

LESTAVOR should not be taken with grapefruit juice.

Hypercholesterolaemia

Heterozygous familial hypercholesterolaemia and mixed dyslipidaemia

The usual starting dose is 10 mg of LESTAVOR daily. The dose may be adjusted at intervals of 4 weeks up to a maximum of 80 mg daily.

Homozygous familial hypercholesterolaemia

10 to 80 mg LESTAVOR once per day. LESTAVOR should be used in these patients as an adjunct to other lipid-lowering treatments such as LDL apheresis, or if such treatments are unavailable.

Prevention of cardiovascular complications

The usual dose is 10 mg LESTAVOR once per day.

Special populations

Dosage in patients with renal insufficiency

Dosage adjustment in patients with renal dysfunction is not necessary because renal

disease does not affect the plasma concentrations nor LDL-C reduction (however, see section 4.4).

Dosage in patients with hepatic impairment

In patients with moderate to severe hepatic dysfunction, the therapeutic response to LESTAVOR is unaffected, but serum levels of the medicine are significantly increased. In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Both C_{max} and AUC are 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 dosing should be exercised in patients who take substantial quantities of alcohol and/or have a history of liver disease (see sections 4.3 and 4.4).

Paediatric population

Treatment experience in the paediatric population is limited.

4.3 Contraindications

- Hypersensitivity to atorvastatin, other HMG-CoA reductase inhibitors or any component of LESTAVOR (see section 6.1).
- Active hepatic disease (the condition may be exacerbated) or unexplained persistently raised serum-aminotransferase concentrations (exceeding 3 times the upper limit of normal).
- Pregnancy and lactation (see section 4.6).
- Patients with Child-Pugh B and C liver impairment.
- Concomitant use with rifampicin, diltiazem and grapefruit juice (see section 4.5).

4.4 Special warnings and precautions for use

Effects on the liver

If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate aetiology is not found, LESTAVOR should not be restarted.

Serum transaminase

Serum transaminase values may be increased, usually to less than 3 times the upper limit of normal, in slightly less than 1 to 2 % of patients receiving HMG-CoA reductase inhibitors for at least 1 year.

Marked increases to more than 3 times the upper limit of normal have occurred.

Liver function tests, including serum transaminase

Determinations are recommended prior to initiation of therapy, following each dosage increase, and subsequently when clinically indicated. LESTAVOR should be discontinued if the rise in transaminase levels is persistent and/or increases to three times the upper limit of normal (ULN) or more.

LESTAVOR should be used with caution in patients who consume substantial amounts of alcohol and/or who have a history of liver disease.

Renal impairment

Renal impairment has no influence on plasma concentrations; therefore dose adjustment is not needed.

LESTAVOR should be used with caution in patients who may be predisposed to developing renal failure secondary to rhabdomyolysis (such as those with severe acute infection, hypotension, severe metabolic, endocrine or electrolyte disorders,

uncontrolled seizures, major surgery or trauma) as well as in patients with severe renal impairment.

There is an increased risk of developing renal failure if rhabdomyolysis occurs (see also "Rhabdomyolysis" under "Skeletal muscle" below).

Skeletal muscle

LESTAVOR may cause myopathy and rhabdomyolysis, especially at higher doses, and it should be used with caution in patients at risk of rhabdomyolysis, and particularly in patients taking medicines, such as cytochrome P450 inhibitors (see section 4.5), that increase plasma concentrations of the HMG-CoA reductase inhibitor, LESTAVOR.

Rhabdomyolysis with or without renal impairment has been reported with the use of HMG-CoA reductase inhibitors such as LESTAVOR. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for the skeletal muscle adverse events.

The onset of rhabdomyolysis may occur weeks to months after initiation of treatment.

General measures to reduce the risk of myopathy

Patients starting treatment with LESTAVOR should be advised of the risk of myopathy and should promptly report unexplained muscle pain, tenderness, or weakness, especially if accompanied by malaise or fever. A creatine kinase (CK) level above 10 times the Upper Limit of Normal (ULN) in a patient, with unexplained symptoms, indicate myopathy. LESTAVOR should be discontinued if creatine phosphokinase increases significantly or if myopathy is diagnosed.

Measures to reduce the risk of myopathy caused by medicine interactions

The benefits of using LESTAVOR concomitantly with immunosuppressants, fibrates or lipid- lowering doses of niacin should be carefully considered. Concomitant administration with ciclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV-protease inhibitors and nefazodone is not recommended. In patients receiving ciclosporin, LESTAVOR should be temporarily discontinued.

Myasthenia gravis or ocular myasthenia

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

Haemorrhagic stroke

Patients without coronary heart disease who had a stroke or transient ischaemic attack (TIA) within the preceding 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 risk for recurrent haemorrhagic stroke.

Lactose intolerance

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

Paediatric patients

Use in paediatric patients is not recommended, as safety and efficacy have not been established.

4.5 Interaction with other medicines and other forms of interaction

Inhibitors of cytochrome P450

Atorvastatin is metabolised by cytochrome P450 3A4. Concomitant administration of LESTAVOR with inhibitors of cytochrome P450 3A4 can lead to an increase in plasma concentrations of atorvastatin.

Medicines that inhibit cytochrome P450 isoenzyme **CYP3A4** include: ciclosporin, itraconazole, ketoconazole, erythromycin/clarithromycin (see Macrolides below), HIV-protease inhibitors, amiodarone, verapamil and nefazodone. There is a similar interaction with grapefruit juice (contra-indicated); see Grapefruit juice below.

Macrolides

Erythromycin/clarithromycin: In healthy individuals plasma concentrations of atorvastatin increased approximately 40 % with co-administration of erythromycin, a known inhibitor of **CYP 3A4**.

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

Grapefruit juice

Co-administration of grapefruit juice and atorvastatin may increase the concentration of atorvastatin, as in LESTAVOR, by 2,5 to 3,3 fold. Therefore the combination should be avoided (see section 4.3).

Inducers of cytochrome P450 3A4

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. Due to the dual mechanism of rifampicin, simultaneous co-administration of LESTAVOR 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).

Cimetidine

Co-administration of atorvastatin with cimetidine does not alter plasma concentration and LDL reduction.

Diltiazem HCl

Co-administration of atorvastatin with diltiazem was associated with a 51 % increase in the AUC of atorvastatin. Therefore the combination should be avoided (see section 4.3).

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 LESTAVOR should be closely monitored and temporary suspension of LESTAVOR may be appropriate.

Transporter Inhibitors

Inhibitors of the OATP1B1 (organic anion-transporting polypeptide-1B1) transport system, such as ciclosporin, can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and ciclosporin 5,2 mg/kg per day resulted in a 7,7 fold increase in exposure to atorvastatin.

Warfarin

A possible increase in the anticoagulant effect of warfarin may occur. Patients taking warfarin should have their INR determined before starting LESTAVOR therapy. The INR should be monitored frequently enough in the early stages of therapy until stabilised. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on warfarin. When there is a dose adjustment of LESTAVOR, this procedure should be repeated.

Digoxin

Concurrent use may cause an elevation in serum digoxin concentrations by approximately 20 %.

Bile acid sequestrants

LESTAVOR should be taken 1 hour before or 4 hours after cholestyramine. Concurrent use may decrease the bioavailability of LESTAVOR.

Azole antifungals, ciclosporin, gemfibrozil, other fibrates, immunosuppressants, macrolide antibiotics or niacin

Concurrent use with LESTAVOR may be associated with an increased risk of myopathy, myositis, rhabdomyolysis and acute renal failure (see section 4.4).

Antacids

Concurrent use may decrease plasma concentrations of atorvastatin by approximately 35 %. LDL-C reduction is however not altered.

Oral contraceptives

Concurrent use with atorvastatin may increase the AUC value for norethindrone and ethinyl oestradiol by approximately 30 % and 20 % respectively.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation have not been established. The use of LESTAVOR during pregnancy and lactation, or in women who plan to become pregnant, is contra-indicated.

Women of child-bearing potential should use appropriate contraceptive measures. In the event of planning a pregnancy, an interval of one month should be allowed from stopping LESTAVOR treatment.

4.7 Effects on ability to drive and use machines

LESTAVOR may cause blurred vision, dizziness and confusion.

Patients should therefore not operate hazardous machinery, including motor vehicles, until they are reasonably certain that LESTAVOR does not adversely affect them.

4.8 Undesirable effects

List of adverse reactions

Blood and lymphatic system disorders

Less frequent: Thrombocytopenia, anaemia, neutropenia.

Immune system disorders

Frequent: Hypersensitivity reactions, including anaphylaxis and angioedema.

Metabolism and nutrition disorders

Less frequent: Hypoglycaemia, hyperglycaemia, weight gain, anorexia.

Psychiatric disorders

Frequent: Insomnia.

Nervous system disorders

Frequent: Dizziness, headache, paraesthesia, hypoaesthesia.

Less frequent: Peripheral neuropathy, cognitive impairment such as memory loss, forgetfulness, amnesia, memory impairment and confusion.

Frequency unknown: Myasthenia gravis.

Eye disorders

Less frequent: Blurred vision, visual disturbance.

Frequency unknown: Ocular myasthenia.

Ear and labyrinth disorders

Less frequent: Tinnitus, hearing loss.

Vascular disorders

Less frequent: Peripheral oedema.

Respiratory, thoracic and mediastinal disorders

Frequency unknown: Sinusitis, pharyngitis.

Gastrointestinal disorders

Frequent: Constipation, diarrhoea, flatulence, heartburn, abdominal pain and cramps, nausea, dyspepsia.

Less frequent: Dysgeusia (taste disturbances), vomiting, pancreatitis, anorexia.

Hepatobiliary disorders

Less frequent: Hepatitis, cholestatic jaundice, hepatic failure.

Skin and subcutaneous tissue disorders

Frequent: Skin rash, pruritus.

Less frequent: Alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, bullous rashes, urticaria.

Musculoskeletal, connective tissue and bone disorders

Frequent: Myalgia, arthralgia, back pain.

Less frequent: Myopathy, characterised by myalgia and muscle weakness, and associated with increased creatine phosphokinase concentrations, rhabdomyolysis with acute renal failure, myositis, muscle cramps, tendon rupture.

Reproductive system and breast disorders

Less frequent: Impotence (decreased sexual ability), gynaecomastia.

General disorders and administration site conditions

Frequent: Fatigue, asthenia, chest pain, infection.

Less frequent: Malaise.

Description of selected adverse reactions

Laboratory test findings

Marked and persistent increases of serum transaminases and elevated alkaline phosphatase and gamma-glutamyl transpeptidase have been reported. Liver function test abnormalities have generally been mild and transient. Increases in serum creatinine kinase (CK) levels, derived from skeletal muscle, have been reported (see section 4.4).

Creatine kinase (CK) concentrations

Mild transient increases are common and may not be medication related. Medication related marked increases, with myositis and possible renal failure occur in about 0,5 to 1 % of patients, although the incidence may be higher in organ transplant patients treated concurrently with immunosuppressants or gemfibrozil.

Determination of serum creatine kinase is recommended if the patient develops muscle tenderness during therapy or during concurrent therapy with niacin or immunosuppressive medications. A level of 10 times higher than the upper limit of normal in a patient with unexplained muscle symptoms indicates myopathy.

Organ transplant with immunosuppressive therapy

Increased risk of rhabdomyolysis and renal failure.

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 Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

See sections 4.4 and 4.8.

General measures should be adopted and liver function should be monitored.

Treatment is symptomatic and supportive. Haemodialysis is not expected to significantly increase atorvastatin (as in LESTAVOR) clearance, due to extensive plasma protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A 7.5 Serum-cholesterol reducers.

Atorvastatin is a fully synthetic cholesterol-lowering medicine. It is a competitive inhibitor of 3- hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol. As a result, in patients with hyperlipidaemias, including hypercholesterolaemias and combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), and dysbetalipoproteinaemia (type III), atorvastatin reduces total plasma cholesterol, low-density lipoprotein (LDL-C)- and very low density lipoprotein (VLDL-C)-cholesterol concentrations, triglycerides and apolipoprotein B. In addition, atorvastatin increases high-density lipoprotein (HDL-C)-cholesterol. Atorvastatin exerts its main effect in the liver.

5.2 Pharmacokinetic properties

Absorption

Atorvastatin is administered in an active (open) form without the need for hydrolysis. It is rapidly absorbed from the gastrointestinal tract, with maximum concentration being achieved in 1 to 2 hours. It has a low absolute bioavailability of the parent compound of about 12 %, due to presystemic clearance in the gastrointestinal mucosa and/or first-pass metabolism in the liver, its primary site of action.

LDL-C reduction is similar whether atorvastatin is given with or without food, despite a decreased rate and extent of absorption when given with food.

LDL-C reduction is the same regardless of the time of administration, despite lower atorvastatin plasma concentrations following evening administration compared to morning administration.

Distribution

Atorvastatin is 98 % or more bound to plasma proteins.

Metabolism

Atorvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4 to a number of active metabolites (ortho- and parahydroxylated derivatives and various beta-oxidation products). The ortho- and parahydroxylated metabolites are pharmacologically active and their *in vitro* inhibition of HMG-CoA reductase activity is equivalent to the parent compound.

Elimination

The mean plasma elimination half-life of atorvastatin is about 14 hours, although the half-life of inhibitory activity for HMG-CoA reductase is about 20 to 30 hours due to the contribution of the active metabolites. Atorvastatin is excreted as metabolites, primarily in the bile. Less than 2 % is excreted renally.

Special populations

Elderly

Lipid lowering effects in the elderly are comparable to those in young adults at equal doses, despite higher plasma concentrations of atorvastatin in healthy elderly subjects.

Paediatrics

Pharmacokinetic data in the paediatric population are not available.

Hepatic impairment

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 section 4.3.

Renal impairment

Renal impairment has no influence on plasma concentrations; therefore dose adjustment is not needed; see section 4.4.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Activated attapulgite.

Microcelac 100 (consisting of lactose monohydrate and microcrystalline cellulose)~~,~~.

Microcrystalline cellulose.

Pregelatinised starch.

Hydroxypropyl cellulose.

Magnesium stearate.

Silica colloidal anhydrous.

Opadry White (consisting of hypromellose, lactose monohydrate, polyethylene glycol and titanium dioxide).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original packaging (in the carton) at or below 30 °C.

6.5 Nature and contents of container

Packs of 28 (4 blisters of 7 tablets) or 30 (3 blisters of 10 tablets) film-coated tablets packed in Aluminium/Aluminium blister strips in a cardboard carton.

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion

0157

8. REGISTRATION NUMBERS

LESTAVOR 10: 44/7.5/1058

LESTAVOR 20: 44/7.5/1059

LESTAVOR 40: 44/7.5/1060

LESTAVOR 80: 44/7.5/1061

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

01 March 2013

10. DATE OF REVISION OF THE TEXT

13 December 2023

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