PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ALIPTO 10 (film-coated tablets)

ALIPTO 20 (film-coated tablets)

ALIPTO 40 (film-coated tablets)

ALIPTO 80 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSTION

ALIPTO 10

Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 10 mg atorvastatin.

Contains sugar: mannitol 70,97 mg per tablet.

Also contains: 2.93 mg of sodium per tablet.

ALIPTO 20

Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 20 mg atorvastatin.

Contains sugar: mannitol 141,94 mg per tablet.

Also contains: 5.86 mg of sodium per tablet.

ALIPTO 40

Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 40 mg atorvastatin.

Contains sugar: mannitol 283,88 mg per tablet.

Also contains: 11.72 mg of sodium per tablet.

ALIPTO 80

Each film-coated tablet contains atorvastatin calcium trihydrate, equivalent to 80 mg atorvastatin.

Contains sugar: mannitol 567,76 mg per tablet.

Also contains: 23.44 mg of sodium per tablet.

ALIPTO 10/ 20/ 40/ 80

Contains Butylated hydroxyanisole as an antioxidant.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Film-coated Tablets.

ALIPTO 10: White colored, oval shaped, biconvex film coated tablets with one side embossed “10” and other side plain.

ALIPTO 20: White colored, oval shaped, biconvex film coated tablets with one side embossed “20” and other side plain.

ALIPTO 40: White colored, oval shaped, biconvex film coated tablets with one side embossed “40” and other side plain.

ALIPTO 80: White colored, oval shaped, biconvex film coated tablets with one side embossed “80” and other side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

a) Hypercholesterolaemia

ALIPTO is indicated:

- As an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglyceride levels in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) and combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate.
- To reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if there are no treatments available.

b) Paediatric Patients (10 – 17 years old)

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

1) LDL-C remains ≥ 190 mg/dℓ (4,98 mmol/ℓ) or

2) LDL-C remains ≥ 160 mg/dℓ (4,04 mmol/ℓ) 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.

c) 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, **ALIPTO** is indicated to reduce the risk of ischaemic cardiovascular and cerebrovascular diseases.

Secondary Prevention

ALIPTO is indicated in the 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 **ALIPTO**, 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

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

The usual starting dose is 10 mg once a day and should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum recommended dose will depend on the indication (see below). Doses may be given any time of the day with or without food.

Primary hypercholesterolaemia and combined hyperlipidaemia

The majority of patients are controlled with 10 mg **ALIPTO** 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 in paediatric patients (> 10 – 17 years old)

Patients should be started with 10 mg **ALIPTO** 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 **ALIPTO**, 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.

Special populations

Dosage in patients with renal insufficiency

Renal disease has no influence on the plasma concentrations or on the lipid effects of **ALIPTO**; thus, no adjustment of dose is required.

Dosage in patients with hepatic dysfunction

In patients with moderate to severe hepatic dysfunction, the therapeutic response to **ALIPTO** 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. Cmax and AUC are each 4-fold greater in patients with Child-Pugh A disease. Cmax and AUC are each 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 4.3 and 4.4).

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to atorvastatin or to any of the ingredients of **ALIPTO**.
- Active liver disease or unexplained persistent increase of serum transaminases exceeding 3 times the upper limit of normal (See 4.4).
- Concomitant use with rifampicin, diltiazem and grapefruit juice.
- Patients with Child-Pugh B and C (liver cirrhosis).
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Liver effects:

It is recommended that liver function tests should be performed before initiating treatment and periodically thereafter. Furthermore, patients who develop any signs or symptoms suggestive of liver injury should also have liver function tests performed.

Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in transaminases (ALT or AST) of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of **ALIPTO** is recommended.

ALIPTO 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 contra-indications to the use of **ALIPTO.**

Muscle Effects:

ALIPTO may affect the skeletal muscle and cause myalgia (generalised muscle pain), myositis (inflammation of muscle tissue), and myopathy (muscle aching or muscle weakness) that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine phosphokinase (CPK) values greater than 10 times the upper limit of normal.

ALIPTO should be discontinued if CPK increases significantly or if myopathy is diagnosed.

The risk of myopathy during treatment with **ALIPTO** is increased with concomitant use of immunosuppressive medicines, including ciclosporin, fibric acid derivatives, nicotinic acid, azole antifungals or erythromycin, and cytochrome P450 inhibitors (See 4.5).

Risk of myasthenia gravis and ocular myasthenia with statin use.

ALIPTO 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).

ALIPTO should be used with caution in patients with renal impairment as the risk of myopathy is increased.

Before the treatment

ALIPTO should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis.

A creatine kinase (CK) level should be measured before starting treatment in the following situations:

- renal impairment
- hypothyroidism
- personal or familial history of hereditary muscular disorders
- previous history of muscular toxicity with a statin or fibrate
- previous history of liver disease and/or where substantial quantities of alcohol are consumed
- in elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.
- situations where an increase in plasma levels may occur, such as interactions and special populations including genetic subpopulations.

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

Creatine kinase measurement

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 times ULN), levels should be re-measured within 5 to 7 days later to confirm the results.

Whilst on treatment

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of **ALIPTO** or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- **ALIPTO** must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Protease inhibitors

Co-administration of **ALIPTO** and protease inhibitors increases plasma concentrations of **ALIPTO.**

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.

Increase in glycosylated haemoglobin (HbAIB) and fasting serum glucose levels have been reported with statin use.

Products containing mannitol may have a laxative effect or cause diarrhoea.

ALIPTO 10/ 20/ 40: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

ALIPTO 80: This medicinal product contains 23.44 mg sodium per tablet equivalent to 1,17 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

The most serious consequence of interactions with **ALIPTO** is the development of myopathy or rhabdomyolysis. Medicines that cause myopathy when given alone increase the risk of myopathy with **ALIPTO**; these medicines include fibric acid derivatives (fibrates or gemfibrozil), and nicotinic acid. The risk of myopathy is also increased by medicines that increase the plasma concentrations of **ALIPTO**, by inhibiting their metabolism or by inhibiting their uptake into the liver.

Inhibitors of cytochrome P450 3A4:

ALIPTO is metabolised by the cytochrome P450 isoenzyme CYP3A4 and interactions may occur with medicines that inhibit this enzyme, including immunosuppressants (ciclosporin), itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors, nefazodone, danazol, amiodarone, and verapamil. There may also be a similar interaction with grapefruit juice. Such combinations should be used with caution, if at all, and dose reduction may be revised.

Rhabdomyolysis may be reported when atorvastatin is given with the non-nucleoside reverse transcriptase inhibitor delavirdine.

Rhabdomyolysis and hepatitis have also been reported in patients receiving atorvastatin with diltiazem.

Inducers of cytochrome P450 3A4:

Concomitant administration of **ALIPTO** with inducers of cytochrome P450 isoenzyme CYP3A4 (e.g. efavirenz, rifampicin, St. John's Wort) can lead to variable reductions in the plasma concentrations of **ALIPTO**. Due to the dual interaction mechanism of rifampicin, simultaneous co-administration of **ALIPTO** with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in **ALIPTO** plasma concentrations.

Antacids:

Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides decreases plasma concentrations of **ALIPTO** approximately 35 %, however, LDL-C reduction is not altered.

Colestipol:

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

Digoxin:

Co-administration of multiple doses of **ALIPTO** and digoxin increased steady-state plasma digoxin concentrations. Patients taking digoxin should be monitored appropriately.

Oral contraceptives:

Co-administration of **ALIPTO** with an oral contraceptive produces increases in plasma concentrations of norethindrone and ethinyl oestradiol.

Warfarin:

Prothrombin time should be determined before starting **ALIPTO** in patients taking warfarin or other oral anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on warfarin or other oral anticoagulants. If the dose of **ALIPTO** is changed or discontinued, the same procedure should be repeated.

4.6 Fertility, pregnancy and lactation

ALIPTO is contraindicated in pregnancy, during breastfeeding and in women of child-bearing potential (See 4.3). Women of child-bearing potential should use appropriate contraceptive measures during treatment. An interval of one month should be allowed from stopping **ALIPTO** treatment to conception in the event of planning a pregnancy.

Treatment with **ALIPTO** should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

4.7 Effects on ability to drive or use machines

The product causes some serious or frequent side effects such dizziness, headache, confusion and memory loss, which may impact the ability to drive or operate machines. Patients should be advised not to drive or use machines until they know how **ALIPTO** affects them.

4.8 Undesirable effects

Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Ear and labyrinth disorders	Less frequent	Tinnitus, hearing loss
Eye disorders	Less frequent	Blurred vision, visual disturbances
	Frequency unknown	Ocular myasthenia
Gastrointestinal disorders	Frequent	Nausea, diarrhoea, abdominal pain, dyspepsia, constipation, flatulence
	Less frequent	Vomiting, eructation, pancreatitis
General disorders and administration site conditions	Frequent	Asthenia, chest pain
	Less frequent	Malaise, peripheral oedema, fatigue, pyrexia
Hepatobiliary disorders	Less frequent	Hepatitis, cholestatic jaundice, hepatic failure
Immune system disorders	Frequent	Allergic reactions (including anaphylaxis), angioedema
Injury, poisoning and procedural complications	Less frequent	Tendon rupture
Metabolism and nutrition disorders	Less frequent	Hypoglycaemia, hyperglycaemia, anorexia, weight gain
Nervous system disorders	Frequent	Hypoaesthesia, paraesthesia, dizziness, headache
	Less frequent	Peripheral neuropathy, amnesia, dysgeusia
	Frequency unknown	Myasthenia gravis
Musculoskeletal and connective tissue disorders	Frequent	Myalgia, arthralgia, back pain
	Less frequent	Myositis, muscle cramps, rhabdomyolysis, myopathy, neck pain, muscle fatigue, tendonopathy, sometimes complicated by rupture
Psychiatric Disorders	Less frequent	Nightmare, insomnia, memory loss, forgetfulness, confusion
Reproductive system and breast disorders	Less frequent	Impotence, gynaecomastia
Skin and subcutaneous tissue disorders	Frequent	Pruritus, rash
	Less frequent	Alopecia, urticaria, bullous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.
Infections and infestations	Frequent	Nasopharyngitis
Investigations	Frequent	Abnormal liver function test, increased blood creatine kinase
	Less frequent	Positive white blood cells urine

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **ALIPTO** is important. It allows continued monitoring of the benefit/risk balance of **ALIPTO**. Health care providers are asked to report any suspected adverse reactions via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Report all side effects to Unimed Healthcare (Pty) Ltd.

By reporting side-effects, you can help provide more information on the safety of **ALIPTO**.

4.9 Overdose

Symptoms

There is no specific treatment available for **ALIPTO** overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance**.**

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Category and Class: A 7.5 Serum-cholesterol reducers

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that is responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Statins exert their major effect by a reduction of low-density lipoprotein (LDL) levels. LDL is formed from VLDL and is catabolised primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin reduces the levels of plasma cholesterol and lipoprotein 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, thereby providing for enhanced uptake and catabolism of LDL-C.

Atorvastatin produces an increase in LDL receptor activity together with a change in the quality of circulating LDL particles. The greater number of LDL receptors on the surface of hepatocytes results in increased removal of LDL from the blood, thereby lowering LDL-C levels.

Atorvastatin lowers total cholesterol (total-C), LDL-C, apolipoprotein B levels 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 including mixed dyslipidaemias.

5.2 Pharmacokinetic properties

Atorvastatin is well absorbed following oral administration where maximum plasma concentrations (Cmax) occur within 1 to 2 hours. The extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95 % to 99 % bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12 % and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30 %. The low systemic availability is due to the 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 Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30 % for Cmax and AUC) following evening administration compared to morning administration. However, there is no change in LDL-C reduction regardless of the time of administration (See 4.2).

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 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 approximately 20 to 30 hours due to the contribution of active metabolites. Less than 2 % of a dose of atorvastatin is excreted in urine following oral administration.

Special populations

Elderly:

Plasma concentrations of atorvastatin are higher (approximately 40 % for Cmax 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 Cmax 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 4.2).

Haemodialysis:

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

Hepatic insufficiency:

Plasma concentrations of atorvastatin are significantly enhanced (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B)(See 4.3).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Mannitol

Sodium Laury Sulfate

Colloidal Anhydrous Silica

Anhydrous Sodium Carbonate

Butylated Hydroxyanisole

Microcrystalline Cellulose

Croscarmellose Sodium

Magnesium Stearate

Film coating:

Septifilm LP 010 (hypromellose, microcrystalline cellulose and stearic acid)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from moisture. Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

ALIPTO 10/20/40/80:

Pack size: 28 tablets or 30 tablets

Tablets are packed in Alu-Alu blister composed of silver opaque Alu-Alu cold form laminate & silver opaque Aluminium foil. Each blister strip contains 7 tablets or 10 tablets. Four blister strips of 7's or three blister strips of 10's are packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road and Bluegum Avenue

Anchorville

Lenasia, 1827

South Africa

8. REGISTRATION NUMBER:

ALIPTO 10: 48/7.5/1206

ALIPTO 20: 48/7.5/1207

ALIPTO 40: 48/7.5/1208

ALIPTO 80: 48/7.5/1209

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORIZATION

Date of registration: 25 November 2016

10. DATE OF REVISION OF THE TEXT

Date of revision: 13 December 2023