PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LIPINORM 10 mg film-coated tablets

LIPINORM 20 mg film-coated tablets

LIPINORM 40 mg film-coated tablets

LIPINORM 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LIPINORM 10 mg: Each tablet contains atorvastatin calcium equivalent to 10 mg atorvastatin.

Contains sugar: lactose monohydrate 33 mg per tablet.

LIPINORM 20 mg: Each tablet contains atorvastatin calcium equivalent to 20 mg atorvastatin.

Contains sugar: lactose monohydrate 66 mg per tablet.

LIPINORM 40 mg: Each tablet contains atorvastatin calcium equivalent to 40 mg atorvastatin.

Contains sugar: lactose monohydrate 132 mg per tablet.

LIPINORM 80 mg: Each tablet contains atorvastatin calcium equivalent to 80 mg atorvastatin.

Contains sugar: lactose monohydrate 264 mg per tablet.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets.

LIPINORM 10 mg: White to off white, oval, biconvex, film-coated tablets plain on both sides.

LIPINORM 20 mg: White to off white, oval, biconvex, film-coated tablets plain on both sides.

LIPINORM 40 mg: White to off white, oval, biconvex, film-coated tablets plain on both sides.

LIPINORM 80 mg: White to off white, oval, biconvex, film-coated tablets plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

LIPINORM is indicated:

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

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

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

Reduction of cardiovascular complications

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

diseases.

Secondary reduction

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

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

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

4.2 Posology and method of administration

Posology

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

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).

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

The majority of patients are controlled with 10 mg LIPINORM 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 LIPINORM 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 LIPINORM, with a greater than 15 % reduction in LDL-C (18 % – 45 %).

Reduction of cardiovascular complications

The dosage range is 10 to 80 mg once daily.

Special populations

Dosage in patients with renal insufficiency

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

Dosage in patients with hepatic dysfunction

In patients with moderate to severe hepatic dysfunction, the therapeutic response to LIPINORM 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 sections 4.3 and 4.4).

Method of administration

LIPINORM is for oral administration.

Doses may be given at any time of day with or without food.

4.3 Contraindications

LIPINORM is contraindicated in patients:

- with hypersensitivity to atorvastatin or to any of the excipients of LIPINORM listed in section 6.1.
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- during pregnancy, while breastfeeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).
- treated with the hepatitis C antivirals glecaprevir/pibrentasvir.
- taking rifampicin, diltiazem and drinking grapefruit juice (see section 4.5).
- patients with Child-Pugh B and C (liver cirrhosis).

4.4 Special warnings and precautions for use

Liver effects

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed.

Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of LIPINORM is recommended (see section 4.8). LIPINORM should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of LIPINORM 80 mg is uncertain, and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).

Skeletal muscle effects

Atorvastatin may affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure. There have been reports of an immune mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Before the treatment

LIPINORM should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin 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 (see section 4.5) and special populations including genetic subpopulations (see section 5.2).

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 remeasured 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 LIPINORM, 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 atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close

monitoring.

- LIPINORM must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicines

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicines that may increase the plasma concentration of atorvastatin such as colchicine, potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, letermovir and HIV protease inhibitors including atazanavir, indinavir, saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir and fosamprenavir plus ritonavir and cytochrome P450 inhibitors). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicines.

In cases where co-administration of these medicines with LIPINORM is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicines that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of LIPINORM should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

LIPINORM 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, statin 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 statins 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. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of LIPINORM and fusidic acid should only be considered on a case by case basis and under close medical supervision.

LIPINORM 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).

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes mellitus

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

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

be monitored both clinically and biochemically according to national guidelines.

Excipients

LIPINORM contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, total lactase deficiency, glucose-galactose malabsorption should not take LIPINORM.

Paediatric population

No clinically significant effect on growth and sexual maturation was observed in children (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Effect of co-administered medicines on atorvastatin

LIPINORM is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. LIPINORM is also identified as a substrate of the multi-medicine resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). Concomitant administration of medicines that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of LIPINORM with other medicines that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.3 and 4.4).

CYP3A4 inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (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) should be avoided if possible. In cases where co-administration of these medicines with LIPINORM cannot be avoided lower starting and maximum doses of LIPINORM should be considered and appropriate clinical monitoring of the patient is recommended.

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with LIPINORM may result in increased exposure to LIPINORM. Therefore, a lower maximum dose of LIPINORM should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

CYP3A4 inducers

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

Transport inhibitors

Inhibitors of transport proteins (e.g. ciclosporin, letermovir) can increase the systemic exposure of atorvastatin. The effect of inhibition of hepatic uptake transporters on

atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended. Use of LIPINORM is not recommended in patients taking letermovir co-administered with ciclosporin (see section 4.4).

Gemfibrozil/ fibric acid derivatives

The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and LIPINORM. If concomitant administration cannot be avoided, the lowest dose of LIPINORM to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).

Ezetimibe

The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and LIPINORM. Appropriate clinical monitoring of these patients is recommended.

Colestipol

Plasma concentrations of atorvastatin and its active metabolites were lower when colestipol was co-administered with LIPINORM. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicine was given alone.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this

combination. If treatment with systemic fusidic acid is necessary, LIPINORM treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Colchicine

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

Antacids

Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides can decrease plasma concentrations of atorvastatin, however, LDL-C reduction will not be altered.

Effect of atorvastatin on co-administered medicines

Digoxin

When multiple doses of digoxin and LIPINORM are co-administered, steady-state digoxin concentrations can increase slightly. Patients taking digoxin should be monitored appropriately.

Oral contraceptives

Co-administration of LIPINORM with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

Warfarin

In patients receiving chronic warfarin therapy, co-administration of LIPINORM daily with warfarin can cause a small decrease in prothrombin time during the first 4 days of dosing which can return to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time

should be determined before starting LIPINORM in patients taking warfarin 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. If the dose of LIPINORM is changed or discontinued, the same procedure should be repeated. LIPINORM therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Paediatric population

Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above-mentioned interactions for adults and the warnings in section 4.4 should be taken into account for the paediatric population.

Grapefruit juice

Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of LIPINORM by 2,5 to 3,3-fold and the combination should be avoided (see section 4.3).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3).

Pregnancy

LIPINORM is contraindicated during pregnancy (see section 4.3). Safety in pregnant women has not been established. Maternal treatment with LIPINORM may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicines during pregnancy should

have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, LIPINORM should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with LIPINORM should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

Breastfeeding

It is unknown whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites were similar to those in milk. Because of the potential for serious adverse reactions, women taking LIPINORM should not breastfeed their infants (see section 4.3). LIPINORM is contraindicated during breastfeeding (see section 4.3).

Fertility

In animal studies atorvastatin had no effect on male or female fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following table presents the adverse reaction profile for LIPINORM

MedDRA system organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Frequent	Infection, flu syndrome, nasopharyngitis

Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Frequent	Allergic reactions
	Less frequent	Anaphylaxis
Metabolism and nutrition disorders	Frequent	Hyperglycaemia
	Less frequent	Hypoglycaemia, weight gain, anorexia
Psychiatric disorders	Less frequent	Nightmare, insomnia
Nervous system disorder	Frequent	Headache
	Less frequent	Dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia, peripheral neuropathy
Eye disorders	Less frequent	Vision blurred, visual disturbance
Ear and labyrinth disorders	Less frequent	Tinnitus, hearing loss
Respiratory, thoracic and mediastinal disorders	Frequent	Sinusitis, pharyngitis, pharyngolaryngeal pain, epistaxis
Gastrointestinal disorders	Frequent	Constipation, flatulence, dyspepsia, nausea, diarrhoea
	Less frequent	Vomiting, abdominal pain upper and lower, eructation, pancreatitis
Hepato-biliary disorders	Less frequent	Hepatitis, cholestasis, hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Urticaria, skin rash, pruritus, alopecia, angioedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal

		necrolysis
Musculoskeletal and connective tissue disorders	Frequent	Myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain
	Less frequent	Neck pain, muscle fatigue, myopathy, myositis, rhabdomyolysis, muscle rupture, tendonopathy, sometimes complicated by rupture, lupus-like syndrome
	Frequency unknown	Immune mediated necrotizing myopathy (see section 4.4)
Reproductive system and breast disorders	Less frequent	Impotence, gynecomastia
General disorders and administration site conditions	Less frequent	Malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia,
Investigations	Frequent	Abnormal liver function test, increased blood creatine kinase
	Less frequent	White blood cells urine positive
Injury, poisoning and procedural complications	Frequency unknown	Accidental injury

Paediatric population

No clinically significant effect on growth and sexual maturation is observed in children. The safety and tolerability profile in paediatric patients are similar to the known safety profile of

atorvastatin in adult patients. Based on data available, the frequency, type and severity of adverse reactions in children is similar to adults.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: Lipid modifying medicines, 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.

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

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

5.2 Pharmacokinetic properties

Absorption

Atorvastatin is absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. 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 attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and absorption by approximately 25 % and 9 % respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30 % for C_{max} and AUC) following evening administration compared to

morning administration of the medicine. However, LDL-C reduction is the same regardless of the time of medicine administration (see section 4.2).

Distribution

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

Biotransformation

Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolised via glucuronidation. *In vitro*, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70 % of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. 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 recovered in urine following oral aministration.

Special populations

Elderly

Plasma concentrations of atorvastatin and its active metabolites are higher (approximately 40 % for C_{max} and 30 % for AUC) in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Gender

Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approximately 20 % higher for C_{max} and approximately 10 % lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal impairment

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

Hepatic impairment

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

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.

SLOC1B1 polymorphism

Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section

4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2,4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

Paediatric population

Oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC are observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (Avicel PH 101), lactose, calcium carbonate, crosscarmellose sodium, polysorbate 80, hydroxypropyl cellulose, magnesium stearate, colour Opadry white.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

The film-coated tablets are packed in Aluminium/Aluminium foil blister strips. The blister strips are packed in cartons containing 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein, Cape Town

7570

8. REGISTRATION NUMBERS

LIPINORM 10 mg: 47/7.5/1151

LIPINORM 20 mg: 47/7.5/1152

LIPINORM 40 mg: 47/7.5/1153

LIPINORM 80 mg: 47/7.5/1154

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 April 2022

10. DATE OF REVISION OF THE TEXT

6 April 2022

LIP/C/PI/A