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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Atorvastatin LHC 20 (Tablets)

Atorvastatin LHC 10 (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Atorvastatin LHC 20: Each tablet contains atorvastatin calcium trihydrate, equivalent to 20 mg atorvastatin

Atorvastatin LHC 10: Each tablet contains atorvastatin calcium trihydrate, equivalent to 10 mg atorvastatin

Contains sugar

Atorvastatin LHC tablets contain lactose monohydrate 113,78 mg per 20 mg tablet and 56,89 mg per 10 mg tablet.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

Atorvastatin LHC 20: White, round, bevel-edged, slightly convex, film-coated tablet, 8 mm in diameter**.**

Atorvastatin LHC 10: White, round, bevel-edged, slightly convex, film-coated tablet, 6 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

Atorvastatin LHC 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

(heterozygous familial) and mixed dyslipidaemia (Fredrickson type IIa and IIb). **Atorvastatin LHC** 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) or if such treatments are unavailable.

Paediatric patients (10 – 17 years of age)

Atorvastatin LHC tablets are used as an adjunct therapy to diet to reduce total-C, LDL-C and apo B levels in boys and postmenarchal girls of > 10 – 17 years of age, with heterozygous familial hyper-cholesterolaemia if after an adequate trial of diet therapy the following findings are present:

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

Prevention of cardiovascular complications

Atorvastatin LHC tablets are indicated to reduce the risk of ischaemic cardiovascular and cerebrovascular diseases in patients without clinically evident cardiovascular disease and with or without dyslipidaemia but with multiple risk factors for coronary heart disease.

Atorvastatin LHC is also indicated for secondary 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 **Atorvastatin LHC** , secondary causes for hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug 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

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

The usual starting dose is 10 mg once a day. Doses should be individualized 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 will depend on the indication (see below). Doses may be given at any time of day with or without food.

Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia

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

Prevention of cardiovascular complications

The dosage range is 10 to 80 mg once daily.

Dosage in Patients with Renal Insufficiency

Renal disease has no influence on the plasma concentrations or on the lipid effects of **Atorvastatin LHC**; 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 **Atorvastatin LHC** 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 approximately 16-

fold and 11-fold increased, respectively, in patients with Childs-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).

4.3 Contraindications

Atorvastatin LHC is contraindicated in patients with:

- Hypersensitivity to atorvastatin or any component of **Atorvastatin LHC** tablets.
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal (see section 4.4).
- Child –Pugh B and C (liver cirrhosis)

Concomitant use with rifampicin, diltiazem and grapefruit juice (see section 4.5).

- Pregnancy and lactation (See section 4.6).
- Treated with the hepatitis C antivirals glecaprevir/pibrentasvir (see section 4.5)

4.4 Special warnings and precautions for use

Liver Effects:

Atorvastatin LHC tablets should not be given to patients with active liver disease or unexplained persistently raised serum aminotransferase concentrations and should be discontinued if marked or persistent increases in serum aminotransferase concentrations occur.

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 transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, withdrawal of atorvastatin is recommended.

Atorvastatin LHC 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 **Atorvastatin LHC** (see section 4.3).

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Skeletal Muscle:

Rhabdomyolysis with or without renal impairment has been reported with the use of **Atorvastatin LHC.** Myalgia has been reported in patients treated with **Atorvastatin LHC** (see section 4.8). Myopathy in conjunction with increases in creatine phosphokinase (CPK) values greater than 10 times the upper limit of normal, should be considered in any patients with diffuse myalgias, muscle tenderness or weakness, and/or market elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Atorvastatin LHC** therapy should be discontinued if elevated CPK levels occur or myopathy is suspected or diagnosed.

The risk of myopathy during treatment with **Atorvastatin LHC** is increased with concurrent use of immunosuppressive medicines such as ciclosporin, fibric acid derivatives and nicotinic acid, azole antifungals or erythromycin, colchicine, the hepatitis C protease inhibitor telaprevir, boceprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir and cytochrome P450 inhibitors (see section 4.5**).**

Medical practitioners considering combined therapy with **Atorvastatin LHC** 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 **Atorvastatin LHC** and fusidic acid. Temporary suspension of **Atorvastatin LHC** may be appropriate during fusidic acid therapy (see section 4.5).

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 Atorvastatin LHC and fusidic acid should only be considered on a case by case basis and under close medical supervision.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Atorvastatin LHC therapy should be discontinued in patients with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders and uncontrolled seizures).

Protease inhibitors:

Concomitant use of **Atorvastatin LHC** with protease inhibitors is associated with increased plasma concentrations of atorvastatin.

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 LIPITOR 80 mg revealed a higher incidence of haemorrhagic stroke compared to placebo. Patients with haemorrhagic stroke on entry appeared to be at increased risk for recurrent haemorrhagic stroke.

Endocrine function:

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

Myasthenia gravis and ocular myastania:

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

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Lactose intolerance:

Atorvastatin LHC tablets contains lactose monohydrate and therefore it should not be administered to patients with rare hereditary problems or history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption e.g. galactosaemia.

4.5 Interaction with other medicines and other forms of interaction

The most serious consequence of interactions with **Atorvastatin LHC** is the development of myopathy or rhabdomyolysis. Medicines that can cause myopathy when given alone increase the risk of myopathy with **Atorvastatin LHC** and all the statins, these medicines include immunosuppressive medicines, including ciclosporin, fibric acid derivatives, nicotinic acid and cytochrome P450 3A4 inhibitors such as macrolide antibiotics, clotrimazole etc. (see section 4.4-Skeletal muscle)

Effect of co-administered medicines on atorvastatin

Atorvastatin 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. Atorvastatin is also identified as a substrate of the multi-drug 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 medicinal products 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 the concomitant administration of atorvastatin with other medicinal products that may induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.4).

Inhibitors of cytochrome P450 3A4:

- **Erythromycin/clarithromycin** – in healthy individuals, plasma concentration of **Atorvastatin LHC** increased approximately by 40 % with concomitant use of **Atorvastatin LHC** and erythromycin.

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- **Combination of protease inhibitors** –The use of **Atorvastatin LHC** with ritonavir + saquinavir (400 mg twice daily) resulted in a 3-fold increase in atorvastatin AUC. Co-administration of **Atorvastatin LHC** 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) resulted in a 5,9 fold increase in atorvastatin AUC (see section 4.4).
  In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of **Atorvastatin LHC** should not exceed 20 mg and should be used with caution.
- **Diltiazem hydrochloride** – concurrent use of **Atorvastatin LHC** with diltiazem was associated with an increase in AUC of 51 % of **Atorvastatin LHC** (see section 4.3).
- **Grapefruit juice** – contains one or more components that inhibits CYP 3A4 and can increase plasma concentrations of **Atorvastatin LHC** by 2,5 to 3,3 fold and combination should be avoided (see section 4.3**)**.
- **Cimetidine -** Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.
- **Itraconazole -** Co-administration of **Atorvastatin LHC** 40 mg, single dose and itraconazole 200 mg, once daily, was associated with a 3,3-fold increase in AUC and a 20 % increase in Cmax.

Inducers of cytochrome P450 3A:

Concomitant use of **Atorvastatin LHC** with inducers of cytochrome P450 (e.g efavirenz, rifampicin) can lead to variable reductions in plasma concentrations of **Atorvastatin LHC**. Due to the dual interaction mechanism of rifampicin, simultaneous administration of **Atorvastatin LHC** with rifampicin is not recommended, as delayed administration of **Atorvastatin LHC** after administration of rifampicin has been associated with significant reduction in **Atorvastatin LHC** plasma concentrations.

Antacid:

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

Antipyrine:

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

Colestipol:

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

Digoxin:

Co-administration of multiple doses of **Atorvastatin LHC** and digoxin increased steady-state plasma digoxin concentrations by approximately 20 %. Patients taking digoxin should be monitored appropriately.

Azithromycin:

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

Oral contraceptives:

Co-administration of **Atorvastatin LHC** and an oral contraceptive increased AUC values of norethindrone and ethinyl estradiol approximately 30 % and 20 %, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin:

Atorvastatin LHC had no clinically significant effect on prothrombin time when administered to patients receiving **Atorvastatin LHC** and warfarin therapy for 2 weeks. Nevertheless, patients receiving **Atorvastatin LHC** should be monitored when **Atorvastatin LHC** is combined with warfarin therapy.

Colchicine:

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

Fusidic acid:

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

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 atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin 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 occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with the concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.

Transport protein 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 atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Atorvastatin LHC is contra-indicated in women of childbearing potential not using adequate contraceptive measures as there is a possibility that it could interfere with foetal sterol synthesis.

There have been a number of reports of congenital abnormalities associated with the use

Atorvastatin LHC tablets.

Pregnancy

Atorvastatin LHC is contra-indicated in pregnancy

An interval of one month should be allowed from stopping Atorvastatin LHC treatment to conception in the event of planning a pregnancy.

Breast-feeding

Atorvastatin LHC is contra-indicated in breastfeeding mothers

Fertility

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

4.7 Effects on ability to drive and use machines

Atorvastatin LHC tablets do not affect ability to drive or operate machines. However, patients should be advised not to drive or use machines until they know how Atorvastatin LHC tablets affect them.

4.8 Undesirable effects

System Organ Class	Frequency		
	Frequent	**Less Frequent**	**Unknown**
Blood and lymphatic system disorders		Thrombocytopenia.	
Metabolism and nutrition disorders		Hyperglycaemia, hypoglycaemia, weight gain, anorexia.	
Psychiatric disorders	Insomnia.	Nightmare	
Nervous system disorders	Headache, hypoaesthesia, paraesthesia, dizziness.	Peripheral neuropathy, dysgeusia, amnesia.	Myasthenia gravis
Ear and labyrinth disorders		Tinnitus, hearing loss	
Immune system disorders	Allergic reactions (including anaphylaxis).		
Gastro-intestinal disorders	Diarrhoea, constipation, flatulence, dyspepsia, abdominal pain, nausea.	Vomiting, eructation, pancreatitis.	
Hepato-biliary disorders		Hepatitis, cholestatic jaundice, hepatic failure	
Skin and subcutaneous tissue	Rash, pruritis.	Alopecia, urticaria, bullous rashes, Stevens-Johnson syndrome, toxic epidermal	

		necrolysis, erythema multiforme, angioneurotic oedema	
Musculoskeletal, connective tissue and bone disorder	Myalgia, arthralgia, asthenia, back pain, pain in extremity, muscle spasms, joint swelling	Muscle cramps, myopathy, myositis, rhabdomyolysis, neck pain, muscle fatigue, muscle rupture, tendinopathy, sometimes complicated by rupture, lupus-like syndrome, immune-mediated necrotizing myopathy.	
Reproductive system and breast disorders		Impotence, gynaecomastia	
General disorders and administration site conditions	Asthenia, chest pain.	Malaise, peripheral oedema, fatigue, pyrexia	
Injury and poisoning		Tendon rapture, lupus-like syndrome	
Infections and infestations	Nasopharyngitis		
Eye disorders		Blurred vision, visual disturbance	Ocular myasthenia
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain, epistaxis		
Investigations	Liver function test abnormal, blood creatine kinase increased	White blood cells urine positive	

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

There is no specific treatment for atorvastatin overdosage.

In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 7.5 Serum-cholesterol reducers.

Atorvastatin is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyses an early, rate limiting step in cholesterol biosynthesis.

Atorvatatin affect blood cholesterol levels by inhibiting hepatic cholesterol synthesis, which results in increased expression for the low-density lipoprotein (LDL) receptor gene. In response to reduced free cholesterol content within hepatocytes, membrane-bound secretion enhancer binding proteins (SEBPs) are cleaved by a protease and translocated to the nucleus.

Higher doses of atorvastatin can also reduce triglyceride levels caused by elevated very low-density lipoprotein (VLDL) levels. Some studies suggest that atorvastatin can reduce LDL levels by enhancing the removal of LDL precursors (VLDL and LDL) and by decreasing hepatic VLDL production.

The liver is its primary site of action and the principal site of cholesterol synthesis and low-density lipoprotein cholesterol (LDL-C) clearance. 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:

After oral administration, intestinal absorption of atorvastatin varies between 30 % and 85 %. After an oral dose, plasma concentration peak in 1 to 4 hours. Atorvastatin has a half-life of about 20 hours;

this may contribute to the greater cholesterol lowering efficacy. Due to extensive first-pass hepatic uptake and / or the pre-systemic clearance in the gastrointestinal mucosa, systemic bioavailability of atorvastatin and its hepatic metabolites varies between 5 % and 30 % of administered dose. The metabolites have some HMG-CoA reductase inhibitor activity.

Although food decreases the rate and extent of atorvastatin 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 atorvastatin administration compared to morning administration. However, LDL-C reduction is the same regardless of the time of atorvastatin administration (see section 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:

Biotransformation occurs in the liver and more than 70 % of metabolites are excreted by the liver with subsequent elimination in the faeces.

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, it does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin (parent substance) in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2 % of a dose of atorvastatin is recovered in urine following oral administration.

Special Populations

Geriatric:

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 impairment:

Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin therefore no dose adjustment is necessary (see section 4.2).

Hepatic impairment:

Plasma concentration of atorvastatin is increased (approximately 16 - fold in Cmax and 11 – fold in AUC) in patients with chronic liver disease (Childs - Pugh B) (see section 4.3).

Haemodialysis:

Although studies have not been conducted in patients with end-stage renal disease, haemodialys is not expected to significantly enhance clearance of atorvastatin since atorvastatin is extensively bound to plasma proteins.

5.3 Preclinical safety

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Microcrystalline cellulose (avicel PH 102)

Hydroxycellulose (molecular weight app. 80 000)

Croscarmelose sodium

Crospovidone type A

Sodium laurilsulfate

Sodium hydroxide

Magnesium hydroxide

Magnesium stearate

Opadry II white 85F28751.

Film coating:

Polyvinyl alcohol

Titanium dioxide E171

Macrogol 3000

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister tray in the original cartoon until required for use.

6.5 Nature and contents of container

Atorvastatin LHC 20 & 10 Tablets are available in blister packs of 30's. Blister packs consist of cold formed OPA/Al/PVC film and aluminium foil.

6.6 Special precautions for disposal and other handling

Not applicable.

7 HOLDER OF CERTIFICATE OF REGISTRATION

LHC Pharmaceuticals (Pty) Ltd

N4 Gateway Industrial Park

553 Willow Park Manor

33 Ghaap Street

Pretoria

0184

8 REGISTRATION NUMBER

Atorvastatin LHC 20 – 45/7.5/0448

Atorvastatin LHC 10 – 45/7.5/0447

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 June 2017

10 DATE OF REVISION OF THE TEXT

10 September 2023