APPROVED PROFESSIONAL INFORMATION FOR HAXTOVAT 10, 20, 40 and 80 mg

SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE

HAXTOVAT 10 mg

HAXTOVAT 20 mg

HAXTOVAT 40 mg

HAXTOVAT 80 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

HAXTOVAT 10: Each film-coated tablet contains 10 mg of Atorvastatin equivalent to 10,825 mg of Atorvastatin calcium Trihydrate USP.

HAXTOVAT 20: Each film-coated tablet contains 20 mg of Atorvastatin equivalent to 21,649 mg of Atorvastatin calcium Trihydrate USP.

HAXTOVAT 40: Each film-coated tablet contains 40 mg of Atorvastatin equivalent to 43,299 mg of Atorvastatin calcium Trihydrate USP**.**

HAXTOVAT 80: Each film-coated tablet contains 80 mg of Atorvastatin equivalent to 86,597 mg of Atorvastatin calcium Trihydrate USP.

Contains sugar “lactose monohydrate”.

HAXTOVAT 10 Contains sugar “lactose monohydrate”.

Each film-coated tablets contains 32,500 mg lactose monohydrate.

HAXTOVAT 20 Contains sugar “lactose monohydrate”.

Each film-coated tablets contains 65,000 mg lactose monohydrate.

HAXTOVAT 40 Contains sugar “lactose monohydrate”.

Each film-coated tablets contains 130,00 mg lactose monohydrate.

HAXTOVAT 80 Contains sugar “lactose monohydrate”.

Each film-coated tablets contains 260,000 mg lactose monohydrate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

HAXTOVAT 10

White to off-white, oval, biconvex film coated tablets debossed with '10' on one side and 'A 53' on other side.

HAXTOVAT 20

White to off-white, oval, biconvex film coated tablets debossed with '20' on one side and 'A 54' on other side.

HAXTOVAT 40

White to off-white, oval, biconvex film coated tablets debossed with '40' on one side and 'A 55' on other side.

HAXTOVAT 80

White to off-white, oval, biconvex film coated tablets debossed with '80' on one side and 'A 56' on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

HAXTOVAT 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):

HAXTOVAT is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, > 10 to 17 years of age, with heterozygous familial hypercholesterolaemia if after

an adequate trial of diet therapy, the following findings are present:

a) LDL-C remains ≥ 4,98 mmol/L (190 mg/dL) or

b) 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, **HAXTOVAT** 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 **HAXTOVAT**, 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 **HAXTOVAT** and should continue on this diet during treatment with **HAXTOVAT**.

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). 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 **HAXTOVAT** 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 **HAXTOVAT** 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 **HAXTOVAT**, 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.

Dosage in patients with renal insufficiency:

Renal disease has no influence on the plasma concentrations or on the lipid effects of **HAXTOVAT**; 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 **HAXTOVAT** 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).

4.3 Contraindications

- Hypersensitivity to atorvastatin or any of the excipients listed in section 6.1.
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal (see section 4.4).
- Concomitant use with rifampicin, diltiazem and grapefruit juice (see section 4.5).
- Patients with Child-Pugh B and C (liver cirrhosis).
- Pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Hepatic impairment:

It is recommended that liver function tests be performed before the initiation of treatment with **HAXTOVAT** and repeated as clinically indicated. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with **HAXTOVAT**, promptly interrupt therapy. If an alternate aetiology is not found, do not restart **HAXTOVAT**.

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 atorvastatin is recommended (see section 4.8).

HAXTOVAT 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 contraindications to the use of **HAXTOVAT** (see section 4.3).

Skeletal muscle effects:

Rhabdomyolysis with or without renal impairment has been reported with the use of atorvastatin as in **HAXTOVAT**. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Myalgia has been reported in patients treated with atorvastatin as in **HAXTOVAT** (see section 4.8). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values greater than 10 times the upper limit of normal, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **HAXTOVAT** therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with **HAXTOVAT** is increased with concurrent administration of immunosuppressive medicines, including ciclosporin, fibric acid derivatives, 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. Medical practitioners considering combined therapy with **HAXTOVAT** 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 as in **HAXTOVAT** and fusidic acid. Temporary suspension of **HAXTOVAT** may be appropriate during fusidic acid therapy (see section 4.5).

HAXTOVAT 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).

Concomitant treatment with other medicinal products

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g.ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole,letermovir and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir,etc). 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) (e.g. boceprevir, telaprevir, elbasvir/grazoprevir, ledipasvir/sofosbuvir),erythromycin, niacin, or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead ofthese medicinal products.

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products 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 atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

Atorvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidicacid 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 **HAXTOVAT** and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Protease inhibitors:

Co-administration of **HAXTOVAT** and protease inhibitors was associated with increased plasma concentrations of **HAXTOVAT**.

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 as in **HAXTOVAT** 80 mg revealed a higher incidence of haemorrhagic stroke compared to placebo. Patients with haemorrhagic stroke or lacunar infarct 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 **HAXTOVAT**.

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

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>30kg/m

2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Paediatric population

No clinically significant effect on growth and sexual maturation was observed in a 3-year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight (see section 4.8).

Excipients:

HAXTOVAT tablets contain lactose monohydrate. Patients with rare hereditary problems or a history of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not receive **HAXTOVAT**

4.5 Interaction with other medicines and other forms of interaction

Effect of co-administered medicinal products on atorvastatin

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organicanion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters P-glycoprotein (P-gp) 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 protein may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.3 and 4.4).

Pharmacodynamic interactions

The risk of myopathy during treatment with **HAXTOVAT** is increased with concurrent administration of immunosuppressive medicines, including ciclosporin, fibric acid derivatives, niacin (nicotinic acid) or cytochrome P450 3A4 inhibitors (macrolide antibiotics e.g. erythromycin, and azole antifungals e.g. clotrimazole) (see section 4.4 – Skeletal muscle).

CYP3A4 inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1and specific information below). 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, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co- administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin 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.

Inhibitors of cytochrome P450 3A4*:*

HAXTOVAT is metabolised by cytochrome P450 3A4. Concomitant administration of **HAXTOVAT** with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of **HAXTOVAT**. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4 (see section 4.4).

CYP3A4 inducers

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John'sWort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of

hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transporter inhibitors:

Inhibitors of the OATP1B1 (e.g. ciclosporin) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin as in **HAXTOVAT** 10 mg and ciclosporin 5,2 mg/kg/day resulted in an 8,7-fold increase in exposure to atorvastatin.

Use of atorvastatin 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 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).

Erythromycin/clarithromycin:

In healthy individuals, plasma concentrations of atorvastatin increased approximately 40 % with co-administration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see section 4.4)

Combination of protease inhibitors:

Plasma concentrations of atorvastatin increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of

HAXTOVAT should be avoided. Concomitant administration of atorvastatin 10 mg single dose with tipranavir 500 mg twice daily plus ritonavir 200 mg twice daily for seven days, resulted in a 9,4-fold increase in atorvastatin AUC and 8,6-fold increase in atorvastatin C_{max}. Atorvastatin did not result in a change in pharmacokinetics of tipranavir plus ritonavir. Concomitant administration of atorvastatin 20 mg single dose with telaprevir 750 mg every eight hours, for 10 days, resulted in a 7,9-fold increase in atorvastatin AUC and 10,6-fold increase in atorvastatin C_{max}.

In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing **HAXTOVAT** and the lowest dose necessary should be used. Concomitant administration of atorvastatin 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) resulted in a 5,9-fold increase in atorvastatin AUC. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of **HAXTOVAT** should not exceed 20 mg and should be used with caution. Concomitant administration of atorvastatin 40 mg once a day for 4 days with saquinavir 400 mg twice daily plus ritonavir 400 mg twice daily for 15 days resulted in a 3,9-fold increase in atorvastatin AUC and 4,3-fold increase in atorvastatin $C_{max.}$ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used. Concomitant administration of atorvastatin 10 mg once a day for 4 days with darunavir 300 mg twice daily plus ritonavir 100 mg twice daily for 9 days resulted in a 3,4-fold increase in atorvastatin AUC and 2,3-fold increase in atorvastatin C_{max}. Concomitant administration of Atorvastatin 10 mg once a day for 4 days with fosamprenavir 1 400 mg twice a day for 14 days resulted in a 2,3-fold increase in atorvastatin AUC and 4,0-fold increase in atorvastatin C_{max}. Atorvastatin resulted in a 1,27-fold increase in fosamprenavir. Concomitant administration of atorvastatin 10 mg once a day for 4 days with fosamprenavir 700 mg twice a day plus ritonavir 100 mg twice a day for 14 days resulted in a 2,5-fold increase in atorvastatin AUC and 2,8-fold increase in atorvastatin C_{max}. Atorvastatin did not result in a change in pharmacokinetics of fosamprenavir 700 mg plus ritonavir.

In patients taking nelfinavir, the dose of **HAXTOVAT** should not exceed 40 mg daily. Concomitant administration of atorvastatin 10 mg once a day for 28 days with nelfinavir 1 250 mg twice a day for 14 days resulted in a 74 % increase in atorvastatin AUC and 2,2-fold increase in atorvastatin C_{max}.

Concomitant administration of atorvastatin 40 mg single dose with boceprevir 800 mg three times a day for 7 days resulted in a 2,3-fold increase in atorvastatin AUC and 2,66-fold increase in atorvastatin C_{max} (see section 4.4 – Skeletal muscle).

Diltiazem hydrochloride:

Co-administration of atorvastatin with diltiazem was associated with an increase in AUC of 51 % of atorvastatin (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 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 C_{max}.

Grapefruit juice:

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

Inducers of cytochrome P450 3A:

Concomitant administration of **HAXTOVAT** with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampicin) can lead to variable reductions in plasma concentrations of **HAXTOVAT**. Due to the dual interaction mechanism of rifampicin, simultaneous co-administration of atorvastatin as in with rifampicin is not recommended, as delayed administration of atorvastatin as in **HAXTOVAT** after administration of rifampicin has been associated with **a** significant reduction in atorvastatin plasma concentrations.

Antacids:

Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides

decreased plasma concentrations of atorvastatin as in **HAXTOVAT** approximately 35 %; however, LDL-C reduction was not altered.

Antipyrine:

Because **HAXTOVAT** 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 as in decreased approximately 25 % when colestipol and atorvastatin were co-administered. However, LDL-C reduction was greater when atorvastatin and colestipol were co-administered than when either medicine was given alone.

Cholestyramine:

No data is available.

Digoxin:

Co-administration of multiple doses of atorvastatin and digoxin increased steady-state plasma digoxin concentrations by approximately 20 %. Patients taking digoxin should be monitored appropriately (see section 4.4).

Azithromycin:

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

Oral contraceptives:

Co-administration of atorvastatin 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 **HAXTOVAT**.

Warfarin:

Atorvastatin as in **HAXTOVAT** had no clinically significant effect on prothrombin/INR time when administered to patients receiving combined atorvastatin and warfarin therapy for two weeks. Nevertheless, patients receiving **HAXTOVAT** should be closely monitored when **HAXTOVAT** 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.

Amlodipine:

Atorvastatin as in **HAXTOVAT** pharmacokinetics were not altered by the co-administration of Atorvastatin 80 mg and amlodipine 10 mg at steady-state.

Fusidic acid:

Although interaction studies with **HAXTOVAT** 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 **HAXTOVAT** treatment may be appropriate.

Other concomitant therapy:

In clinical studies, atorvastatin was used concomitantly with antihypertensive medicines and oestrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific medicines have not been conducted.

4.6 Fertility, pregnancy and lactation

Pregnancy

HAXTOVAT is contraindicated in pregnancy, in mothers breastfeeding their infants and in women of childbearing potential not using adequate contraceptive measures. **HAXTOVAT** should be administered to women of childbearing age only when such patients are using adequate

contraception and have been informed of the potential hazards to the foetus. An interval of one month should be allowed from stopping **HAXTOVAT** treatment to conception in the event of planning a pregnancy.

Breastfeeding:

Because of the potential for serious adverse reactions, women taking atorvastatin should not breast-feed their infants (see section 4.3). Atorvastatin 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.

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

4.8 Undesirable effects

a) Summary of the safety profiles

The following additional adverse events have been reported in **HAXTOVAT**

MedDRA SOC Organ system	Frequent	Less frequent	Frequency unknown
Infections and infestations	allergic reactions	anaphylaxis.	---
Blood and the lymphatic system disorders	---	Thrombocytopenia	---
Immune system disorders	Allergic reactions (including anaphylaxis)	---	---

Injury and poisoning	---	Tendon rupture	---
Metabolism and nutrition disorders	---	Hypoglycaemia, hyperglycaemia, anorexia, weight gain	
Psychiatric disorders	Insomnia	---	---
Nervous system disorders	Hypoaesthesia, paraesthesia, dizziness, headache	Peripheral neuropathy, amnesia, dysgeusia	
Eye disorders	---	vision blurred, visual disturbance.	---
Ear and labyrinth disorders	---	Tinnitus	
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain, epistaxis.	---	---
Gastrointestinal disorders	Nausea, diarrhoea, abdominal pain, dyspepsia, constipation, flatulence	Pancreatitis, Vomiting	---
Hepato-billiary disorder	---	Hepatitis, cholestatic jaundice	---
Skin and subcutaneous tissue disorders	Pruritus, rash	Alopecia, urticaria, Bullous rashes, Stevens-Johnson syndrome, toxic	---

		epidermal necrolysis, erythema multiforme	
Musculoskeletal, connective tissue and bone disorders	Myalgia, arthralgia, back pain	Myositis, muscle cramps, Rhabdomyolysis, myopathy	---
Reproductive system and breast disorders	---	Impotence	---
General disorders and administrative site conditions	Asthenia, chest pain,	Peripheral oedema, fatigue, Malaise	---
Investigations	liver function test abnormal, blood creatine kinase increased.	white blood cells urine positive.	---

Paediatric patients:

Patients treated with **HAXTOVAT** had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections.

Post-marketing reports:

There have been post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness amnesia, memory impairment, confusion) and immune-mediated necrotizing myopathy associated with use of **HAXTOVAT**.

These side effects may be reversible upon discontinuation of treatment.

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 to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no specific treatment for **HAXTOVAT** overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive medicine binding to plasma proteins, haemodialysis is not expected to significantly enhance **HAXTOVAT** clearance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: Lipid modifying medicines, HMG-CoA-reductase inhibitors,

ATC code: C10AA05

Mechanism of Action

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:

Following oral administration, maximum plasma concentrations occur within 1 to 2 hours. The absolute bioavailability of atorvastatin (parent substance) is approximately 12 % and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30 %. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of 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 litres. Atorvastatin is 98 % or more bound to plasma proteins.

Biotransformation:

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.

Elimination:

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.

Atorvastatin 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 efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), which may limit he intestinal absorption and biliary clearance of atorvastatin.

Special populations:

Elderly:

Plasma concentrations of atorvastatin are higher (approximately 40 % for C_{max} 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 C_{max} 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 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).

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.

Hepatic insufficiency:

Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B) (see section 4.3).

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.

6. Pharmaceutical particulars

6.1 List of excipients

- Microcrystalline Cellulose,
- Carbonate Carbonate
- Lactose Monohydrate
- Croscarmellose Sodium
- Hydroxypropyl Cellulose,
- Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

HAXTOVAT 10 mg

90's Count HDPE Container

High Density Polyethylene Container 40 cc with 33 mm Neck (Heavy weight)

Pack size: 90 film coated tablets.

1000's Count HDPE Container

High Density Polyethylene Container 250 cc with 53 mm Neck (Heavy weight)

with child resistant plastic caps with pulp liners 53 mm and a 2,0 g, Molecular sieve desiccant canister.

Pack size: 1000 film coated tablets.

Blister pack 10 X10's Alu-Alu

Forming: Cold forming (60 microns PVC / 45 Microns Aluminium foil / 25 micro OPA), width 108 mm

Lidding Foil: 25 µ Plain aluminium foil (Hard Tempered) with 7 GSM HSL coating on bright side, width 108 mm

HAXTOVAT 20 mg

90's Count HDPE Container

HDPE container 60 cc with 33 mm neck (Heavy weight), with child resistant plastic caps with pulp liners 33 mm and Silica gel desiccant canister a 2,0 g,

Pack size: 90 film coated tablets.

1000's Count HDPE Container

HDPE container 250 cc with 53 mm neck (Heavy weight), with child resistant plastic caps with pulp

liners 53 mm and a 2,0 g, Molecular sieve desiccant canister.

Pack size: 1000 film coated tablets.

Blister pack 10 X10's Alu-Alu

Forming Cold form foil (60 microns PVC / 45 microns Aluminium foil /25 microns OPA), width 139 mm

Lidding Foil: 25 µ Plain Aluminium foil (Hard Tempered) with 7 GSM HSL coating on bright side, width 139 mm

HAXTOVAT 40 mg

90's Count HDPE Container

HDPE container 120 cc with 38 mm neck (Heavy weight), with child resistant plastic caps with pulp liners 38 mm and Silica gel desiccant canister a 2,0 g,

Pack size: 90 film coated tablets.

500's Count HDPE Container

HDPE container 500 cc with 53 mm neck (Heavy weight), with child resistant plastic caps with pulp liners 53 mm and a 2,0 g, Molecular sieve desiccant canister.

Pack size: 500 film coated tablets.

Blister pack 10 X10's Alu-Alu

Forming Cold form foil (60 microns PVC / 45 microns Aluminium foil /25 microns OPA), width 139 mm

Lidding Foil: 25 µ Plain Aluminium foil (Hard Tempered) with 7 GSM HSL coating on bright side, width 139 mm

HAXTOVAT 80 mg

90's Count HDPE Container

HDPE container 200 cc with 38 mm neck (Heavy weight), with child resistant plastic caps with pulp liners 38 mm and Silica gel desiccant canister a 2,0 g,

Pack size: 90 film coated tablets.

500's Count HDPE Container

HDPE container 950 cc with 53 mm neck (Heavy weight), with child resistant plastic caps with pulp liners 53 mm and a 2,0 g, Molecular sieve desiccant canister.

Pack size: 500 film coated tablets.

Blister pack 10 X10's Alu-Alu

Forming Cold form foil (60 microns PVC / 45 microns Aluminium foil /25 microns OPA), width 148 mm

Lidding Foil: 25 µ Plain Aluminium foil (Hard Tempered) with 7 GSM HSL coating on bright side, width 148 mm

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

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8 REGISTRATION NUMBER (S)

HAXTOVAT 10: 57/7.5/0895

HAXTOVAT 20: 57/7.5/0896

HAXTOVAT 40: 57/7.5/0897

HAXTOVAT 80: 57/7.5/0898

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 JULY 2026

10 DATE OF REVISION OF THE NEXT