1.3.1.1 PROFESSIONAL INFORMATION (CLEAN AMENDED PROPOSED)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Atorvastatin 10 mg Alkem film-coated tablets

Atorvastatin 20 mg Alkem film-coated tablets

Atorvastatin 40 mg Alkem film-coated tablets

Atorvastatin 80 mg Alkem film-coated tablets

Atorvastatin (as calcium)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

Contains Sugar.

Excipient(s) with known effect:

Atorvastatin 10 mg Alkem: Each film-coated tablet contains 31.25 mg of lactose monohydrate.

Atorvastatin 20 mg Alkem : Each film-coated tablet contains 62.50 mg of lactose monohydrate.

Atorvastatin 40 mg Alkem: Each film-coated tablet contains 125.00 mg of lactose monohydrate.

Atorvastatin 80 mg Alkem 80: Each film-coated tablet contains 250.00 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablet.

Atorvastatin 10 mg Alkem: White elliptical shaped, film-coated tablets, debossed with “10” on one side and "ATS" on other side.

Atorvastatin 20 mg Alkem: White elliptical shaped, film-coated tablets, debossed with “20” on one side and "ATS" on other side.

Atorvastatin 40 mg Alkem: White elliptical shaped, film-coated tablets, debossed with “40” on one side and "ATS" on other side.

Atorvastatin 80 mg Alkem: White elliptical shaped, film-coated tablets, debossed with “80” on one side and "ATS" on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

Atorvastatin Alkem is indicated:

1. 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,

2. 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 Alkem 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, **Atorvastatin Alkem** 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 **Atorvastatin Alkem**, 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

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

Posology:

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:

Most patients are controlled with **Atorvastatin Alkem** 10 mg 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 Alkem** 10 mg daily; the maximum recommended dose is 20 mg/day.

Homozygous familial hypercholesterolaemia:

Most patients responded to a dose of **Atorvastatin Alkem** 80 mg, with a greater than 15 % reduction in LDL-C (18 % – 45 %).

Reduction of cardiovascular complications:

The dosage range is 10 mg 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 Alkem**; 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 Alkem** 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 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 4.4).

Method of administration:

For oral use.

4.3 Contraindications

Atorvastatin Alkem is contraindicated in:

- Patients exhibiting hypersensitivity to the atorvastatin or to any of the excipients of **Atorvastatin Alkem**, 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),
- Patients treated with the hepatitis C antivirals glecaprevir/ pibrentasvir,
- Pregnancy and Lactation (see Section 4.6).

4.4 Special warnings and precautions for use

Liver effects:

Persistent elevations (> 3 times the upper limit of normal (ULN) which occurred on 2 or more occasions) in serum transaminases occurred in 0,7 % of patients who received atorvastatin, as in Atorvastatin Alkem, in clinical trials. The incidence of these abnormalities was 0,2 %, 0,2 %, 0,6 % and 2,3 % for 10, 20, 40 and 80 mg respectively. It is recommended that liver function tests be performed before the initiation of treatment with Atorvastatin Alkem and repeated as clinically indicated. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with **Atorvastatin Alkem**, promptly interrupt therapy. If an alternate aetiology is not found, do not restart **Atorvastatin Alkem**. **Atorvastatin Alkem** 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 **Atorvastatin Alkem** (see Section 4.3).

Haemorrhagic stroke:

Patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA), within the precedind 6 months, and who were initiated on atorvastatin 80 mg, exhibited a high incidence of haemorrhagic stroke. The increased risk is evident 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 atorvastatin 80 mg is uncertain, and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).

Skeletal muscle:

Rhabdomyolysis with or without renal impairment has been reported with the use of **Atorvastatin Alkem**. 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 Alkem** (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. **Atorvastatin Alkem** therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with **Atorvastatin Alkem** 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 **Atorvastatin Alkem** 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 Alkem** and fusidic acid. Temporary suspension of **Atorvastatin Alkem** may be appropriate during fusidic acid therapy (see section 4.5).

Atorvastatin Alkem 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).

Protease inhibitors:

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

Endocrine function:

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

Excipients:

Patients with rare hereditary problems of galactose intolerance, total lactose deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

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

Inhibitors of cytochrome P450 3A4:

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4), concomitant administration of medicines that are inhibitors of CYP3A4 may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4 (see section 4.4).

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and 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 medicines with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin 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. 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.

Transport inhibitors:

Inhibitors of transport proteins (e.g., ciclosporin, letermovir) may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. 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).

Erythromycin/clarithromycin:

Plasma concentrations of **Atorvastatin Alkem** increased approximately 40 % when co-administered with erythromycin, a known inhibitor of cytochrome P450 3A4 (see section 4.4 – Skeletal muscle).

Combination of protease inhibitors:

Plasma concentrations of atorvastatin increased significantly when co-administered with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of **Atorvastatin Alkem** alone. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of **Atorvastatin Alkem** should be avoided. Concomitant administration of **Atorvastatin Alkem** 10 mg single dose with tipranavir 500 mg twice daily plus ritonavir 200 mg twice daily for seven days, resulted in significant increase in atorvastatin AUC and Cmax. **Atorvastatin Alkem** does not change in pharmacokinetics of tipranavir plus ritonavir. Concomitant administration of **Atorvastatin Alkem** 20 mg single dose with telaprevir 750 mg every eight hours, for 10 days, resulted in similar increases in atorvastatin AUC and Cmax.

Caution should be used when prescribing **Atorvastatin Alkem** in patients taking the HIV protease inhibitor lopinavir plus ritonavir, and the lowest dose necessary should be used. Concomitant administration of **Atorvastatin Alkem** 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 **Atorvastatin Alkem** should not exceed 20 mg and should be used with caution. Concomitant administration of **Atorvastatin Alkem** 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 Cmax. 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 Alkem** 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 Cmax. Concomitant administration of **Atorvastatin Alkem** 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 Cmax. **Atorvastatin Alkem** resulted in a 1,27-fold increase in fosamprenavir. Concomitant administration of **Atorvastatin Alkem** 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 Cmax. **Atorvastatin Alkem** did not result in a change in pharmacokinetics of fosamprenavir 700 mg plus ritonavir.

In patients taking nelfinavir, the dose of **Atorvastatin Alkem** should not exceed 40 mg daily. Concomitant administration of **Atorvastatin Alkem** 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 Cmax.

Concomitant administration of **Atorvastatin Alkem** 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 Cmax (see section 4.4 – Skeletal muscle).

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

Colestipol:

Plasma concentrations of atorvastatin and its active metabolites were lower (ratio of atorvastatin concentration: 0.74) when colestipol was co-administered with **Atorvastatin Alkem**. However, lipid effects were greater when **Atorvastatin Alkem** 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, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Colchicine:

Cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Diltiazem:

Co-administration of **Atorvastatin Alkem** with diltiazem was associated with an increase in AUC of 51 % of **Atorvastatin Alkem** (see Section 4.4).

Cimetidine:

Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

Itraconazole:

Co-administration of **Atorvastatin Alkem** 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.

Grapefruit juice:

Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of **Atorvastatin Alkem** by 2,5 to 3,3-fold and the combination should be avoided (see Section 4.4).

Digoxin:

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations increased slightly.

Patients taking digoxin should be monitored appropriately.

Oral contraceptives:

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

Warfarin:

Patients receiving chronic warfarin therapy, co-administration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only less

frequent cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Inducers of cytochrome P450 3A:

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

Antacids:

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

Antipyrine:

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

Azithromycin:

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

Amlodipine:

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

Other concomitant therapy:

Atorvastatin Alkem used concomitantly with antihypertensive medicines and oestrogen replacement therapy does not show significant adverse interactions.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential:

Atorvastatin Alkem contraindicated in women of child-bearing potential not using adequate contraceptive measures. **Atorvastatin Alkem** should be administered to women of child-bearing 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 **Atorvastatin Alkem** treatment to conception in the event of planning a pregnancy.

Pregnancy:

Atorvastatin Alkem contraindicated in pregnancy.

Breast-feeding:

Atorvastatin Alkem contraindicated in mothers breastfeeding their infants.

4.7 Effects on ability to drive and use machines

Some adverse effects (e.g., dizziness, blurred vision and visual disturbances) may impair the patient's ability to drive or operate or use machines.

4.8 Undesirable effects

Frequencies of reactions are ranked according to the following convention: *Frequent; less frequent and frequency unknown.* not known (cannot be estimated from the available data).

Infections and infestations:

Frequent: nasopharyngitis.

Less frequent: infection and flu syndrome

Blood and lymphatic system disorders:

Less frequent: thrombocytopenia.

Injury and poisoning:

Less frequent: accidental injury

Immune system disorders:

Frequent: allergic reactions.

Less frequent: anaphylaxis.

Metabolism and nutrition disorders:

Frequent: hyperglycaemia.

Less frequent: hypoglycaemia, weight gain and anorexia.

Psychiatric disorders:

Less frequent: nightmare and insomnia.

Nervous system disorders:

Frequent: headache.

Less frequent: dizziness, paraesthesia, hypoaesthesia, dysgeusia, amnesia and peripheral neuropathy.

Eye disorders:

Less frequent: vision blurred and visual disturbance.

Ear and labyrinth disorders:

Less frequent: tinnitus and hearing loss.

Respiratory, thoracic and mediastinal disorders:

Frequent: pharyngo-laryngeal pain, epistaxis, sinusitis and pharyngitis.

Gastrointestinal disorders:

Frequent: constipation, flatulence, dyspepsia, nausea and diarrhoea.

Less frequent: vomiting, abdominal pain upper and lower, eructation, pancreatitis.

Hepatobiliary disorders:

Less frequent: hepatitis, cholestasis and hepatic failure.

Skin and subcutaneous tissue disorders:

Frequent: skin rash

Less frequent: urticaria, pruritus, alopecia, angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders:

Less frequent: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain, neck pain, muscle fatigue, myopathy, myositis, rhabdomyolysis, muscle rupture, tendonopathy, sometimes complicated by rupture and lupus-like syndrome.

Frequency unknown: immune mediated necrotizing myopathy (see section 4.4).

Reproductive system and breast disorders:

Less frequent: erectile dysfunction, gynecomastia, and impotence.

General disorders and administration site conditions:

Less frequent: malaise, asthenia, chest pain, peripheral oedema, fatigue, and pyrexia.

Investigations:

Frequent: liver function test abnormal, blood creatine kinase increased.

Less frequent: white blood cells urine positive.

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving **Atorvastatin Alkem**. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8 % patients on atorvastatin as in **Atorvastatin Alkem**. These elevations were dose related and were reversible in all patients. Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal may occur on patients on atorvastatin**,** like

other HMG-CoA reductase inhibitors. Levels above 10 times the normal upper range may occur in 0.4 % atorvastatin-treated patients (see section 4.4).

Paediatric population

Paediatric patients aged from 10 to 17 years of age treated with atorvastatin had infections as the most frequent adverse experience.

Growth and sexual maturation were not affected when assessed using Tanner Stage tool, and measurement of height and weight. The safety profile in this group is similar to that in 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. Healthcare professionals 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 Alternatively all adverse events can be reported to Ascend Laboratories vial the e-mail: pharmacist.rsa@Alkem.com.

4.9 Overdose

Specific treatment is not available for **Atorvastatin Alkem** 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 atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 7.5 Serum-cholesterol reducer.

ATC Code: C10AA05 Lipid modifying agents, HMG-CoA-reductase inhibitors.

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.

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.

Clinical Efficacy and Safety

The bioequivalence study indicated that **Atorvastatin Alkem** is bioequivalent to the reference product with respect to the rate and extent of absorption in healthy adult male human subjects under fasting condition.**Atorvastatin Alkem** was well tolerated by all subjects.

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 Cmax and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30 % for Cmax and AUC) following evening administration compared to morning administration 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 para-hydroxylated 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.

Characteristics in special population patients

Elderly:

Plasma concentrations of atorvastatin are higher (approximately 40 % for Cmax and 30 % for AUC) in healthy elderly subjects (65 years and older) than in young adults. LDL-C reduction is comparable to that seen in younger patient populations given equal doses of atorvastatin.

Gender:

Plasma concentrations of atorvastatin in women differ (approximately 20 % higher for Cmax and 10 % lower for AUC) from those in men; however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal impairment:

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 DOSAGE AND

DIRECTIONS FOR USE). 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 impairment:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Other ingredients are calcium carbonate, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polysorbate 80 and coating solution (Opadry White YS-1-7040).

The coating solution is made up of hypromellose, macrogol, talc and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister in outer carton until required for use.

Keep bottle tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Atorvastatin Alkem is packed into plain aluminium/ aluminium blister strips containing 10 tablets in an outer carton.

Atorvastatin Alkem is also packed in a white HDPE bottle with a child resistant or non-child resistant cap. A desiccant is enclosed in the bottle. The bottles contain either 90 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in

accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ascend Laboratories (Pty) Ltd.

R21 Corporate Park

121 Sovereign Drive

Block A, Office 202

Irene Ext.30, Centurion

0157

8. REGISTRATION NUMBER(S)

550608

550609

550610

550611

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 August 2023

10. DATE OF REVISION OF THE TEXT

To be allocated by authority.