SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aztor 10/20/40

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Aztor 10

Each film-coated tablet contains:

Atorvastatin Calcium Trihydrate USP

equivalent to Atorvastatin..... 10mg. Excipients.....q.s. Aztor 20

Each film-coated tablet contains:

Atorvastatin Calcium Trihydrate USP

Equivalent to Atorvastatin.....20mg. Excipients.....q.s. Aztor 40

Each film-coated tablet contains:

Atorvastatin Calcium Trihydrate USP equivalent to Atorvastatin..... 40 mg. Excipients.....q.s. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated Tablets

4. CLINICAL PARTICULARS 1

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia Aztor Tablets is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of

the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate. Aztor Tablets is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable. Prevention of cardiovascular disease Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

4.2 Posology and method of administration

Aztor Tablets is available in the strengths of 10 mg, 20 mg and 40 mg and may not be suitable for all dosage recommendations given below. Therefore, other suitable available strengths and dosage forms of atorvastatin should be used in such cases. Posology The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin. The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response. The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

• Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

The majority of patients are controlled with atorvastatin 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

• Heterozygous familial hypercholesterolaemia

Patients should be started with atorvastatin 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

• Homozygous familial hypercholesterolaemia

Only limited reported data has been reported. The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily. Atorvastatin

should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

• Prevention of cardiovascular disease

In reported primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

• Renal impairment

No adjustment of dose is required (see section 4.4).

• Hepatic impairment

Atorvastatin should be used with caution in patients with hepatic impairment (see section 4.4 and 5.2). Atorvastatin is contraindicated in patients with active liver disease (see section 4.3).

• Co-administration with other medicines

In patients taking hepatitis C antiviral agents elbasvir/grazoprevir or letermovir for cytomegalovirus infection prophylaxis concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20 mg/day (see section 4.4 and 4.5). Use of atorvastatin is not recommended in patients taking letermovir coadministered with ciclosporin (see section 4.4 and 4.5).

• Elderly

Efficacy and safety in patients older than 70 using recommended doses are similar to those reported in the general population.

• Paediatric population

Hypercholesterolaemia Paediatric use should only be carried out by physicians experienced in the treatment of paediatric hyperlipidaemia and patients should be re-evaluated on a regular basis to assess progress. For patients with Heterozygous Familial Hypercholesterolemia aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day. The dose may be increased to 80 mg daily, according to the response and tolerability. Doses should be individualised according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more. The dose titration to 80 mg daily is supported by reported study

data in adults and by limited clinical data from reported studies in children with Heterozygous Familial Hypercholesterolemia (see section 4.8). There are limited safety and efficacy data reported in children with Heterozygous Familial Hypercholesterolemia between 6 to 10 years of age derived from reported open-label studies. Atorvastatin is not indicated in the treatment of patients below the age of 10 years. Currently reported data are described in sections 4.8 and 5.2 but no recommendation on a posology can be made. Method of Administration Aztor Tablets is for oral administration. Each daily dose of atorvastatin is given all at once. Aztor Tablets can be chewed or swallowed whole with a drink of water, and can be taken at any time of day, with or without food.

4.3 Contraindications

Atorvastatin is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients

listed in section 6.1

- with active liver disease or unexplained persistent elevations of serum

transaminases exceeding 3 times the upper limit of normal

- during pregnancy, while breast-feeding and in women of child-bearing

potential not using appropriate contraceptive measures (see section 4.6)

- treated with the hepatitis C antivirals glecaprevir/pibrentasvir

4.4 Special warnings and precautions for use

Hepatic Impairment Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies)

resolve. Should an increase in transaminases of greater than 3 times the upper

limit of normal (ULN) persist, reduction of dose or withdrawal of atorvastatin is recommended (see section 4.8). Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver

disease. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) In a reported post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly reported 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. Skeletal muscle effects Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure. There have been very rare reports of an immune mediated necrotizing myopathy

(IMNM) during or after treatment with some statins. IMNM is clinically

characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment, positive anti-HMG CoA reductase antibody and improvement with immunosuppressive agents.

• Before the treatment

Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin

treatment in the following situations:

- Renal impairment

- Hypothyroidism

- Personal or familial history of hereditary muscular disorders

- Previous history of muscular toxicity with a statin or fibrate

- Previous history of liver disease and/or where substantial quantities of alcohol are

consumed

- In elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis

- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2) In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

• Creatine kinase measurement

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

• Whilst on treatment

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.

- If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.

- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.

- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

- Atorvastatin must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected. Concomitant treatment with other 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) (boceprevir, telaprevir, elbasvir/grazoprevir, ledipasvir/sofosbuvir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these 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 fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of atorvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision. Paediatric population No clinically significant effect on growth and sexual maturation has been reported 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). 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/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. Myasthenia gravis In few cases, statins have been reported to induce de novo or aggravate preexisting myasthenia gravis or ocular myasthenia (see section 4.8). Aztor Tablets should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported. Excipients Aztor Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. BRAND NAME contains sodium. less than 1 mmol sodium (23 mg) per vial that is to say essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin Co-administered Atorvastatin medicinal product and Dose (mg) Ratio Clinical dosing regimen of Recommendation# & AUC Glecaprevir 400 mg 10 mg OD for 8.3 Co-administration with OD/ Pibrentasvir 120 7 days products containing mg OD, 7 days glecaprevir or pibrentasvir is contraindicated (see section 4.3). Tipranavir 500 mg 40 mg on day 9.4 In cases where co- BID/ Ritonavir 200 mg 1, 10 mg on administration with BID, 8 days (days 14 day 20 atorvastatin is necessary, do to 21) not exceed 10 mg atorvastatin Telaprevir 750 mg 20 mg, SD 7.9 daily. Clinical monitoring of q8h, 10 days these patients is Ciclosporin 5.2 10 mg OD for 8.7 recommended. mg/kg/day, stable dose 28 days Lopinavir 400 mg 20 mg

OD for 5.9 In cases where co- BID/ Ritonavir 100 mg 4 days administration with BID, 14 days atorvastatin is necessary, Clarithromycin 500 80 mg OD for 4.5 lower maintenance doses of mg BID, 9 days 8 days atorvastatin are

recommended. At atorvastatin

doses exceeding 20 mg, clinical monitoring of these patients is recommended. Saquinavir 400 mg 40 mg OD for 3.9 In cases where co- BID/ Ritonavir (300 4 days administration with mg BID from days 5- atorvastatin is necessary, 7, increased to 400 mg lower maintenance doses of BID on day 8), days 4- atorvastatin are 18, 30 min after recommended. At atorvastatin atorvastatin dosing doses exceeding 40 mg, Darunavir 300 mg 10 mg OD for 3.4 clinical monitoring of these BID/ Ritonavir 100 mg 4 days patients is recommended. BID, 9 days Itraconazole 200 mg 40 mg SD 3.3 OD, 4 days Fosamprenavir 700 mg 10 mg OD for 2.5 BID/ Ritonavir 100 mg 4 days BID, 14 days Fosamprenavir 1400 10 mg OD for 2.3 mg BID, 14 days 4 days Elbasvir 50 mg OD/ 10 mg SD 1.95 The dose of atorvastatin Grazoprevir 200 mg should not exceed a daily OD, 13 days dose of 20 mg during coadministration with products Co-administered Atorvastatin medicinal product and Dose (mg) Ratio Clinical dosing regimen of Recommendation# AUC& containing elbasvir or grazoprevir. Letermovir 480 mg 20 mg SD 3.29 The dose of atorvastatin OD, 10 days should not exceed a daily dose of 20 mg during co administration with products containing letermovir. Nelfinavir 1250 mg 10 mg OD for 1.74 No specific recommendation. BID, 14 days 28 days Grapefruit Juice, 240 40 mg, SD 1.37 Concomitant intake of large mL OD * quantities of grapefruit juice and atorvastatin is not recommended. Diltiazem 240 mg OD, 40 mg, SD 1.51 After initiation or following 28 days dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended. Erythromycin 500 mg 10 mg, SD 1.33 Lower maximum dose and QID, 7 days clinical monitoring of these patients is recommended. Amlodipine 10 mg, 80 mg, SD 1.18 No specific recommendation. single dose Cimetidine 300 mg 10 mg OD for 1.00 No specific recommendation. QID, 2 weeks 2 weeks Colestipol 10 g BID, 40 mg OD for 0.74** No specific recommendation 24 weeks 8 weeks Antacid suspension of 10 mg OD for 0.66 No specific recommendation. magnesium and 15 days aluminium hydroxides, 30 mL

QID, 17 days Efavirenz 600 mg OD, 10 mg for 3 0.59 No specific recommendation. 14 days days Rifampin 600 mg OD, 40 mg SD 1.12 If co-administration cannot be

7 days (co- avoided, simultaneous co-

administered) administration of atorvastatin

Rifampin 600 mg OD, 40 mg SD 0.20 with rifampin is

5 days (doses recommended, with clinical

separated) monitoring.

Gemfibrozil 600 mg 40 mg SD 1.35 Lower starting dose and BID, 7 days clinical monitoring of these patients is recommended. Fenofibrate 160 mg 40 mg SD 1.03 Lower starting dose and OD, 7 days clinical monitoring of these patients is recommended. Boceprevir 800 mg 40 mg SD 2.3 Lower starting dose and TID, 7 days clinical monitoring of these Co-administered Atorvastatin medicinal product and Dose (mg) Ratio Clinical dosing regimen of Recommendation# AUC& patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir. & Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone). # See section 4.4 and section 4.5 for clinical significance. * Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice also reported to result in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold. ** Ratio based on a single sample taken 8-16 h post dose. OD = once daily; SD = single dose; BID = twice daily; TID = three times daily; QID = four times daily. Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products Atorvastatin and Co-administered medicinal product dosing regimen Medicinal product/Dose Ratio Clinical

(mg) of Recommendation

AUC& 80 mg OD for 10 Digoxin 0.25 mg OD, 20 1.15 Patients taking digoxin days days should be monitored appropriately. 40 mg OD for 22 Oral contraceptive OD, 2 1.28 No specific recommendation. days months 1.19

- norethindrone 1 mg

-ethinyl estradiol 35 µg 80 mg OD for 15 * Phenazone, 600 mg SD 1.03 No specific recommendation. days

10 mg, SD Tipranavir 500 mg 1.08 No specific recommendation.

BID/ritonavir 200 mg BID, 7 days

10 mg, OD for 4 Fosamprenavir 1400 mg 0.73 No specific recommendation.

days BID, 14 days

10 mg OD for 4 Fosamprenavir 700 mg 0.99 No specific recommendation.

days BID/ritonavir 100 mg BID, 14 days & Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone). * Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone. OD = once daily; SD = single dose; BID = twice daily.

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3). Pregnancy Atorvastatin is contraindicated during pregnancy (see section 4.3). Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been reported in pregnant women. There have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase

inhibitors. Studies in animals have reported toxicity to reproduction (see section

5.3). Maternal treatment with atorvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia. For these reasons, atorvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are

pregnant. Treatment with atorvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3). Lactation It is unknown whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are reported to be similar to those in milk (see section 5.3). 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 breast-feeding (see section 4.3). Fertility In reported animal studies, atorvastatin had no effect on male or female fertility (see section 5.3).

4.6 Fertility, pregnancy and lactation

Not provided in the source SmPC.

4.7 Effects on ability to drive and use machines

Atorvastatin has been reported to have negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Based on data from reported clinical studies and extensive reported postmarketing experience, below is the adverse reaction profile for atorvastatin. Estimated frequencies of reactions are ranked according to the following convention: common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the reported data). Infections and infestations Common: nasopharyngitis. Blood and lymphatic system disorders Rare: thrombocytopenia. Immune system disorders Common: allergic reactions. Very rare: anaphylaxis. Metabolism and nutrition disorders Common: hyperglycaemia. Uncommon: hypoglycaemia, weight gain, anorexia. Psychiatric disorders Uncommon: nightmare, insomnia. Nervous system disorders Common: headache. Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia. Rare: peripheral neuropathy. Not known: myasthenia gravis. Eye disorders Uncommon: vision blurred. Rare: visual disturbance. Not known: ocular myasthenia. Ear and labyrinth disorders Uncommon: tinnitus. Very rare: hearing loss. Respiratory, thoracic and mediastinal disorders Common: pharyngolaryngeal pain, epistaxis. Gastrointestinal disorders Common: constipation, flatulence,

dyspepsia, nausea, diarrhoea. Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis. Hepatobiliary disorders Uncommon: hepatitis. Rare: cholestasis. Very rare: hepatic failure. Skin and subcutaneous tissue disorders Uncommon: urticaria, skin rash, pruritus, alopecia. Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. Musculoskeletal and connective tissue disorders Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain. Uncommon: neck pain, muscle fatigue. Rare: myopathy, myositis, rhabdomyolysis, muscle rupture, tendonopathy, sometimes complicated by rupture. Very rare: lupus-like syndrome Not known: immune mediated necrotizing myopathy (see section 4.4). Reproductive system and breast disorders Very rare: gynecomastia. General disorders and administration site conditions Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia. Investigations Common: liver function test abnormal, blood creatine kinase increased. Uncommon: white blood cells urine positive. As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (>3 times upper normal limit) elevations in serum transaminases have been reported to occur in 0.8% patients on atorvastatin. These elevations have been reported to be dose related and reversible in all patients. Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin, similar to other HMG-CoA reductase inhibitors in reported clinical trials. Levels above 10 times the normal upper range were reported 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 an adverse experience profile generally reported to be similar to that of patients treated with placebo, the most common adverse experiences reported in both groups, regardless of causality assessment, were infections. No clinically significant effect on growth and sexual maturation was reported in a 3-year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight. The safety and tolerability profile in paediatric patients was reported to be similar to the known safety profile of atorvastatin in adult patients. Based on the data reported, the

frequency, type and severity of adverse reactions in children is reported to be similar to adults.

The following adverse events have been reported with some statins:

• Sexual dysfunction.

• Depression.

• Exceptional cases of interstitial lung disease, especially with long term therapy

(see section 4.4).

• Diabetes Mellitus: Frequency will depend on the presence or absence of risk

factors (fasting blood glucose ≥5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

4.9 Overdose

Specific treatment is not available for atorvastatin 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

Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA-reductase inhibitors, ATC code: C10AA05. Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the ratelimiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutarylcoenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the receptor with high affinity to LDL (LDL receptor). Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the

liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipidlowering medicinal products. Atorvastatin has been reported to reduce concentrations of total-C (30% - 46%), LDL-C (41% - 61%), apolipoprotein B (34% - 50%), and triglycerides (14% - 33%) while producing variable increases in HDL-C and apolipoprotein A1 in a reported dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus. Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

5.2 Pharmacokinetics properties

Absorption Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (Cmax) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is reported as 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. Distribution Mean volume of distribution of atorvastatin is reported as approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins. Biotransformation Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolised via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites has been reported to be equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-

CoA reductase is attributed to active metabolites. Elimination Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic

metabolism. However, atorvastatin does not appear to undergo significant

enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is reported as approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is reported as approximately 20 to 30 hours due to the contribution of active metabolites. 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 the intestinal absorption and biliary clearance of atorvastatin. Special populations Elderly Plasma concentrations of atorvastatin and its active metabolites are reported to be higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those reported in younger patient populations. Paediatric population In a reported open-label, 8-week study, Tanner Stage 1 and Tanner Stage ≥2 paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C ≥ 4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily,

respectively. Body weight was the only significant covariate in atorvastatin

population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were reported over the range of atorvastatin and ohydroxyatorvastatin exposures. Gender Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for Cmax and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women. Renal impairment Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites. Hepatic impairment Plasma concentrations of atorvastatin and its active metabolites are reported to be markedly increased (approx. 16-fold in Cmax and approx. 11-fold in

AUC) in patients with chronic alcoholic liver disease (Child-Pugh B). 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.

5.2 Pharmacokinetic properties

Not provided in the source SmPC.

5.3 Preclinical safety data

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of reported in vitro tests and in vivo assay. Atorvastatin was not reported to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) reported hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from reported animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or foetuses. In rats, rabbits and dogs, atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal toxicity was reported in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is reported evidence of placental transfer. In rats, plasma concentrations of atorvastatin are reported to be similar to those in milk. It is not reported whether atorvastatin or its metabolites are excreted in human milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core: Calcium carbonate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, polysorbate, hydroxypropyl cellulose, magnesium stearate, opadry white, simethicone emulsion and wax candelilla.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture

6.5 Nature and contents of container

Aztor Tablets are available in cold form blister of 10's pack.

6.6 Special precautions for disposal and other handling

No Special Requirement.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING

SITE ADDRESS Sun Pharmaceutical Industries Limited

8. MARKETING AUTHORISATION NUMBER(S)

14635/R1

9. DATE OF FIRST REGISTRATION/ RENEWAL OF THE REGISTRATION

2026 August 31

10. DATE OF REVISION OF THE TEXT

2026 August 31