**SUMMARY OF PRODUCT CHARACTERISTICS**

**STORVAS**
(Atorvastatin Tablets 10 mg, 20 mg)

## 1. NAME OF THE MEDICINAL PRODUCT

**STORVAS**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**STORVAS**
Each film-coated tablet contains:
Atorvastatin equivalent to
Atorvastatin ..... 10/20 mg
Excipients ..... q.s.

For the full list of excipients, see **section 6.1.**

## 3. PHARMACEUTICAL FORM

Film coated Tablets

## 4. CLINICAL PARTICULARS[1]

### 4.1 Therapeutic indications

***Hypercholesterolaemia***

Atorvastatin 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 nonpharmacological measures is inadequate.

Atorvastatin 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

***Dose***

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 co-administered 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.

Other pharmaceutical forms/strengths may be more appropriate for this population.

Method of Administration

STORVAS is for oral administration. Each daily dose of atorvastatin is given all at once and may be given 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 of the formulation
- 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

***Liver effects***

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of 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.

- *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

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

***Excipients***
STORVAS contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products 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, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein

(BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see **section 5.2**). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at 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**).

*CYP3A4 inhibitors*
Potent CYP3A4 inhibitors have been reported 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 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 reported with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been reported. 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.

*CYP3A4 inducers*
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) 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.

*Transport inhibitors*
Inhibitors of transport proteins (e.g. ciclosporin, letermovir) can increase the systemic exposure of atorvastatin (see **Table 1**). 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 (see **Table 1**).

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**).

*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 reported to be lower (ratio of atorvastatin concentration: 0.74) when colestipol was co-administered with atorvastatin. However, lipid effects were reported to be greater when atorvastatin and colestipol were co-administered than when either medicinal product 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*
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.

***Effect of atorvastatin on co-administered medicinal products***

*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 with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

*Warfarin*
In a reported clinical study in 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 very rare 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.

*Paediatric population*
Reported drug-drug interaction studies have only been reported in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings in WARNINGS AND PRECAUTIONS should be taken into account for the paediatric population.

*Drug interactions*

**Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin**

| Co-administered | Atorvastatin |
|---|---|

| **medicinal product and dosing regimen** | **Dose (mg)** | **Ratio of AUC[&]** | **Clinical Recommendation[#]** |
|---|---|---|---|
| Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7 days | 10 mg OD for 7 days | 8.3 | Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see **section 4.3**). |
| Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21) | 40 mg on day 1, 10 mg on day 20 | 9.4 | In cases where co-administration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended. |
| Telaprevir 750 mg q8h, 10 days | 20 mg, SD | 7.9 | |
| Ciclosporin 5.2 mg/kg/day, stable dose | 10 mg OD for 28 days | 8.7 | |
| Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days | 20 mg OD for 4 days | 5.9 | In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended. |
| Clarithromycin 500 mg BID, 9 days | 80 mg OD for 8 days | 4.5 | |
| Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 4-18, 30 min after atorvastatin dosing | 40 mg OD for 4 days | 3.9 | In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended. |
| Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days | 10 mg OD for 4 days | 3.4 | |
| Itraconazole 200 mg OD, 4 days | 40 mg SD | 3.3 | |
| Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days | 10 mg OD for 4 days | 2.5 | |
| Fosamprenavir 1400 mg BID, 14 days | 10 mg OD for 4 days | 2.3 | |
| Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days | 10 mg SD | 1.95 | The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing elbasvir or grazoprevir. |
| Letermovir 480 mg OD, 10 days | 20 mg SD | 3.29 | The dose of atorvastatin 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. |

| Co-administered medicinal product and dosing regimen | Atorvastatin | | |
|---|---|---|---|
| | Dose (mg) | Ratio of AUC[&] | Clinical Recommendation[#] |
| BID, 14 days | 28 days | | |
| Grapefruit Juice, 240 mL OD * | 40 mg, SD | 1.37 | Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended. |
| Diltiazem 240 mg OD, 28 days | 40 mg, SD | 1.51 | After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended. |
| Erythromycin 500 mg QID, 7 days | 10 mg, SD | 1.33 | Lower maximum dose and clinical monitoring of these patients is recommended. |
| Amlodipine 10 mg, single dose | 80 mg, SD | 1.18 | No specific recommendation. |
| Cimetidine 300 mg QID, 2 weeks | 10 mg OD for 2 weeks | 1.00 | No specific recommendation. |
| Colestipol 10 g BID, 24 weeks | 40 mg OD for 8 weeks | 0.74** | No specific recommendation |
| Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 17 days | 10 mg OD for 15 days | 0.66 | No specific recommendation. |
| Efavirenz 600 mg OD, 14 days | 10 mg for 3 days | 0.59 | No specific recommendation. |
| Rifampin 600 mg OD, 7 days (co-administered) | 40 mg SD | 1.12 | If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring. |
| Rifampin 600 mg OD, 5 days (doses separated) | 40 mg SD | 0.20 | |
| Gemfibrozil 600 mg BID, 7 days | 40 mg SD | 1.35 | Lower starting dose and clinical monitoring of these patients is recommended. |
| Fenofibrate 160 mg OD, 7 days | 40 mg SD | 1.03 | Lower starting dose and clinical monitoring of these patients is recommended. |
| Boceprevir 800 mg TID, 7 days | 40 mg SD | 2.3 | Lower starting dose and clinical monitoring of these 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 dosing regimen** | **Co-administered medicinal product** | | |
|---|---|---|---|
| | **Medicinal product/Dose (mg)** | **Ratio of AUC[&]** | **Clinical Recommendation** |
| 80 mg OD for 10 days | Digoxin 0.25 mg OD, 20 days | 1.15 | Patients taking digoxin should be monitored appropriately. |
| 40 mg OD for 22 days | Oral contraceptive OD, 2 months<br>- norethindrone 1 mg<br>-ethinyl estradiol 35 µg | 1.28<br>1.19 | No specific recommendation. |
| 80 mg OD for 15 days | * Phenazone, 600 mg SD | 1.03 | No specific recommendation. |
| 10 mg, SD | Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days | 1.08 | No specific recommendation. |
| 10 mg, OD for 4 days | Fosamprenavir 1400 mg BID, 14 days | 0.73 | No specific recommendation. |
| 10 mg OD for 4 days | Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days | 0.99 | No specific recommendation. |

[&] 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 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**).

## 4.7 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 post-marketing 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.

***Eye disorders***
*Uncommon*: vision blurred.
*Rare*: visual disturbance.

***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/$m^2$, 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[1]

## 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 rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme 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 lipid-lowering 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 ($C_{max}$) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. 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 multi-drug resistance protein 1 (MDR1) 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 o-hydroxyatorvastatin exposures.

*Gender*
Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for $C_{max}$ 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 $C_{max}$ 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.

### 5.3 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 $AUC_{0-24h}$ 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

Microcrystalline cellulose, Lactose monohydrate, Colloidal anhydrous silica, Croscarmellose sodium, Sodium bicarbonate, Sodium carbonate anhydrous, Hydroxypropyl cellulose, Butylated hydroxy anisole, Butylated hydroxy toluene, Isopropyl alcohol, Magnesium stearate, Opadry YS-I-7040 white.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 Months

### 6.4 Special precautions for storage

Store below 30$^{o}$C

### 6.5 Nature and contents of container

Blister Foil

### 6.6 Special precautions for disposal and other handling

Not applicable

## 7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Limited
Sun House, 201 B/1,
Western Express Highway,
Goregaon (East),
Mumbai - 400063 India

## 8. MARKETING AUTHORISATION NUMBER(S)

NAFDAC Reg. No.: 04-8144 & 04-8146

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21-12-2005

## 10. DATE OF REVISION OF THE TEXT

January 2021

## REFERENCES

1. Summary of product characteristics of Lipitor 10 mg film-coated tablets, Upjohn UK Limited, July 2020.

***Lipitor*** is the registered trademark of ***Upjohn UK Limited*** and is not a trademark of Sun Pharmaceutical Industries Ltd. The maker of this brand is not affiliated with and does not endorse Sun Pharmaceutical Industries Ltd. or its products.