



## Module 1 Administrative and Product Information

### FRESHBORN ATORVASTATIN CALCIUM TABLETS

#### Atorvastatin Calcium Tablets USP 20 mg

### 1.3 PRODUCT INFORMATION

#### 1.3.1 Summary of Product Characteristics (SmPC)

##### 1. Name of the Medicinal Product

Atorvastatin Calcium Tablets USP 20 mg

##### 2. Qualitative and Quantitative Composition

###### Each film coated Tablet Contains:

Atorvastatin Calcium USP Eq. to

Atorvastatin ..... 20 mg

Excipients ..... QS

Colour: Titanium Dioxide

##### 3. Pharmaceutical Form

Film coated tablet.

###### Description

White coloured, biconvex, round shaped, film coated tablet having both sides plain.

##### 4. Clinical Particulars

#### 4.1 Therapeutic Indications

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.



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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

### 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 data are available.

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. In the 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.

#### Hepatic impairment



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Atorvastatin should be used with caution in patients with hepatic impairment. Atorvastatin is contraindicated in patients with active liver disease.

#### Co-administration with other medicines

In patients taking hepatitis C antiviral agents elbasvir/grazoprevir concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20 mg/day.

#### Elderly

Efficacy and safety in patients older than 70 using recommended doses are similar to those seen 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 study data in adults and by limited clinical data from studies in children with Heterozygous Familial Hypercholesterolemia.

There are limited safety and efficacy data available in children with Heterozygous Familial Hypercholesterolemia between 6 to 10 years of age derived from open-label studies. Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

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

#### Method of administration

Atorvastatin 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.



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#### 4.3 Contraindications

Atorvastatin is contraindicated in patients:

- With hypersensitivity to the active substance or to any of the excipients of this Medicinal product.
- 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.
- 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 recommended.

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 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 hemorrhagic stroke in patients initiated on Atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunars infarct at study entry. For patients with prior hemorrhagic stroke or lacunars infarct, the balance of risks and benefits of Atorvastatin 80 mg is uncertain and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment.

##### Skeletal muscle effects



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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 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 remeasured within 5 to 7 days later to confirm the results.



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#### 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  $\leq 5 \times$  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 ( $> 10 \times$  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. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, erythromycin, niacin and 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.



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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. 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 in 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 was observed in a 3-year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight.

#### Interstitial lung disease

Exceptional cases of interstitial lung disease may be reported with some statins, especially with long term therapy. 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 > 30 kg/m<sup>2</sup>, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.



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#### Excipients

Atorvastatin contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactose deficiency or glucosegalactose 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 metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. 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 derivatives and ezetimibe.

#### CYP3A4 inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole 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.

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin. An increased risk of myopathy may be 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





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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) can increase the systemic exposure of atorvastatin. The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended.

#### 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.

#### 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.

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Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was coadministered with Atorvastatin. However, lipid effects were 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.

#### Colchicine

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

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 clinical study in patients receiving chronic warfarin therapy, coadministration 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 may be seen, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough



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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

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings should be taken into account for the paediatric population.

## 4.6 Pregnancy and lactation

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment.

#### Pregnancy

Atorvastatin is contraindicated during pregnancy. Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction. Maternal treatment with atorvastatin may reduce the fetal 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.

#### Breast feeding



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It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk. Because of the potential for serious adverse reactions, women taking Atorvastatin should not breast-feed their infants. Atorvastatin is contraindicated during breastfeeding.

#### 4.7 Effects on ability to drive and use machines

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

#### 4.8 Undesirable effects

The adverse events seen with atorvastatin tablets are generally mild and transient. The frequencies of adverse events are ranked according to the following: Common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $\leq 1/10,000$ ).

Infections and infestations:

Common:

nasopharyngitis.

Blood and lymphatic system

disordersRare: 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.



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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, StevensJohnson 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, tendonopathy, sometimes complicated by rupture. Very rare: lupus-like syndrome.

Not known: immune-mediated necrotizing myopathy

Reproductive system and breast disorders

Very rare: gynecomastia.

General disorders and administration site conditions

Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.



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#### 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 may be seen 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 occurred in 0.8% patients on Atorvastatin. 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 occurred in 2.5% of patients on Atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% Atorvastatin-treated patients.

#### Paediatric population

Paediatric patients aged from 10 to 17 years of age treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. No clinically significant effect on growth and sexual maturation was observed in a 3- year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight. The safety and tolerability profile in paediatric patients was similar to the known safety profile of atorvastatin in adult patients. The following adverse events may be seen with some statins:

- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy.
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose  $\geq 5.6$  mmol/L, BMI  $> 30$  kg/m<sup>2</sup>, raised triglycerides, history of hypertension).



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#### **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.



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## 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 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 hypercholesterolemia, a population that has not usually responded to lipid-lowering medicinal products.

Atorvastatin has been shown 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 dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, non-familial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulindependent diabetes mellitus.

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

Homozygous familial hypercholesterolaemia





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In a multicenter 8 week open-label compassionate-use study with an optional extension phase of variable length, 335 patients were enrolled, 89 of which were identified as homozygous familial hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDL-C was approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

#### Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid- Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomised double- blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

A compassionate use study in patients with severe hypercholesterolaemia (including homozygous hypercholesterolaemia) included 46 paediatric patients treated with atorvastatin titrated according to response. The study lasted 3 years: LDL-cholesterol was lowered by 36%. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

## 5.2 Pharmacokinetic properties

### Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. Atorvastatin tablets are bioequivalent to atorvastatin solutions. The absolute bioavailability of atorvastatin 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.

### Distribution



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Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is 98% bound to plasma proteins.

#### Biotransformation

Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. 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, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

#### **Special Populations**

**Elderly:** Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

**Paediatric:** In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage  $\geq 2$  (N=24) paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C  $\geq 4$  mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of filmcoated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric population appeared similar to adults when scaled all metrically by body weight. Consistent decreases in LDL-C and TC may be observed over the range of atorvastatin and ohydroxy atorvastatin exposures.

**Gender:** Concentrations of atorvastatin and its active metabolites in women differ from those in men (women: approximately 20% higher for C<sub>max</sub> and 10% lower for AUC).



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These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Hepatic Insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approximately 16-fold in C<sub>max</sub> and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

SLC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLC1B1 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 (SLC1B1 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 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC<sub>0-24h</sub> reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic; however, at maternally toxic doses fetal toxicity was observed 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 evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

**Module 1 Administrative and Product Information****FRESHBORN ATORVASTATIN CALCIUM TABLETS****Atorvastatin Calcium Tablets USP 20 mg****6. Pharmaceutical Particulars****6.1 List of Excipients**

Lactose, Microcrystalline Cellulose-102, P.V.P.K-30, Colloidal Silicon Dioxide, Magnesium Stearate and DR COAT HSP.

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf Life**

36 months

**6.4 Special Precautions for Storage**

Store below 30°C. Protect from heat & moisture.

**6.5 Nature and Contents of Container**

10 Tablets are packed in Alu-Alu Blister. Such 3 blisters are packed in one inner carton with package insert.

**6.6 Special Precautions for Disposal and Other Handling**

Not applicable.

**7.0 Marketing Authorisation Holder****Manufactured by:**

CLAROID PHARMACEUTICAL PVT. LTD.

Survey No. 217/P Opp. Gurukul English Medium

School Kamod, Satpanth Mandir Pirana Rd,

TA, Ahmedabad- 382425, Gujarat, India

**8.0 Marketed by:**

FRESHBORN INDUSTRIES LIMITED

45 Ashogbon Street Idumota,, Lagos State