TRUVA™

(Atorvastatin Calcium)

1. NAME OF THE PRODUCT

TRUVA™ (Atorvastatin Calcium) 10mg Tablet
TRUVA™ (Atorvastatin Calcium) Tablet 20mg
TRUVA™ (Atorvastatin Calcium) Tablet 40mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRUVA™ 10mg Tablet
Each film coated tablet contains:
Atorvastatin Calcium Trihydrate USP
equivalent to Atorvastatin.....10mg

TRUVA™ Tablet 20mg
Each film coated tablet contains:
Atorvastatin Calcium Trihydrate USP
equivalent to Atorvastatin.....20mg

TRUVA™ Tablet 40mg
Each film coated tablet contains:
Atorvastatin Calcium Trihydrate USP
equivalent to Atorvastatin.....40mg

3. PHARMACEUTICAL FORM

Film coated tablet

Appearance:
TRUVA™ 10mg Tablet: Red oval film coated tablet, plain on one side and break line on other side.
TRUVA™ Tablet 20mg: Green round film coated tablet, plain on both sides.
TRUVA™ Tablet 40mg: Red oval film coated tablet, plain on one side and break line on other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Hypercholesterolaemia: TRUVA™ 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.

TRUVA™ 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:

Posology:

The patient should be placed on a standard cholesterol-lowering diet before receiving **TRUVA™** and should continue on this diet during treatment with **TRUVA™**. The dose should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response. The usual starting dose is 10mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80mg once a day.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia: The majority of patients are controlled with **TRUVA™** 10mg 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 **TRUVA™** 10mg daily. Doses should be individualized and adjusted every 4 weeks to 40mg daily. Thereafter, either the dose may be increased to a maximum of 80mg daily or a bile acid sequestrant may be combined with 40mg **TRUVA™** once daily.

Homozygous familial hypercholesterolaemia: The dose of **TRUVA™** in patients with homozygous familial hypercholesterolemia is 10 to 80mg daily. **TRUVA™** 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 the primary prevention trials the dose was 10mg/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: TRUVA™ should be used with caution in patients with hepatic impairment. **TRUVA™** is contraindicated in patients with active liver disease.

Co-administration with other medicines: In patients taking the hepatitis C antiviral agents elbasvir/grazoprevir or letermovir for cytomegalovirus infection prophylaxis concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20mg/day. Use of **TRUVA™** is not recommended in patients taking letermovir co-administered with ciclosporin.

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 hyperlipidemia 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 **TRUVA™** is 10mg per day. The dose may be increased to 80mg daily, according to response and tolerability. Doses should be individualized according to the recommended goal of therapy. Adjustment should be made at intervals of 4 weeks or more. **TRUVA™** 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:

TRUVA™ is for oral administration.

Each daily dose of **TRUVA™** 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.
- 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:

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. 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): For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80mg 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 characterized 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.

Myasthenia gravis: In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. Atorvastatin should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

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
- Situation 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.

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.
- In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. Atorvastatin Tablets should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Concomitant treatment with other medicinal products: Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, letermovir and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (e.g., boceprevir, telaprevir, elbasvir/grazoprevir, ledipasvir/sofosbuvir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead 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. 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 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 Tablets and fusidic acid should only be considered on a case-by-case basis and under close medical supervision. The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors (e.g., atorvastatin) and daptomycin. Consideration should be given to temporarily suspend Atorvastatin Tablets in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. If co-administration cannot be avoided, CK levels should be measured 2-3 times per week and patients should be closely monitored for any signs or symptoms that might represent myopathy.

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 have been 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 6.9mmol/L, BMI>30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Excipients: Atorvastatin Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

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

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, 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. Moderate CYP3A4 inhibitors (e.g., erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. 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.

Transporter inhibitors: Inhibitors of transport proteins can increase the systemic exposure of atorvastatin. Ciclosporin and letermovir are both inhibitors of transporters involved in the disposition of atorvastatin, i.e., OATP1B1/1B3, P-gp, and BCRP leading to an increased systemic exposure of atorvastatin. The effect of inhibition of hepatic uptake transporters on atorvastatin exposure in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended. Use of

atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin.

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.

Colestipol: Plasma concentrations of atorvastatin and its active metabolites were lower (ratio of atorvastatin concentration: 0.74) when colestipol was co-administered 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 have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Daptomycin: Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g., atorvastatin) co-administered with daptomycin. If co-administration cannot be avoided, appropriate clinical monitoring is recommended.

Effect of atorvastatin on co-administered medicinal products:

Digoxin: When multiple doses of digoxin and 10mg 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: 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. 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.

Drug interactions:

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

Glecaprevir and Pibrentasvir: Co-administration with products containing glecaprevir or pibrentasvir is contraindicated.

Tipranavir and Ritonavir: In cases where co-administration with atorvastatin is necessary, do not exceed 10mg atorvastatin daily. Clinical monitoring of these patients is recommended.

Telaprevir and Ciclosporin: In cases where co-administration with atorvastatin is necessary, do not exceed 10mg atorvastatin daily. Clinical monitoring of these patients is recommended.

Lopinavir, Ritonavir and Clarithromycin: In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20mg, clinical monitoring of these patients is recommended.

Saquinavir, Ritonavir, Darunavir, Itraconazole and Fosamprenavir: In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40mg, clinical monitoring of these patients is recommended.

Elbasvir, Grazoprevir: The dose of atorvastatin should not exceed a daily dose of 20mg during co-administration with products containing elbasvir or grazoprevir.

Letermovir: The dose of atorvastatin should not exceed a daily dose of 20mg during co-administration with products containing letermovir.

Nelfinavir: No specific recommendation.

Grapefruit Juice: Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.

Diltiazem: After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.

Erythromycin: Lower maximum dose and clinical monitoring of these patients is recommended.

Amlodipine: No specific recommendation.

Cimetidine: No specific recommendation.

Colestipol: No specific recommendation.
Antacid suspension of magnesium and aluminium hydroxides: No specific recommendation.
Efavirenz: No specific recommendation.
Rifampin: If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.
Gemfibrozil: Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate: Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir: Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20mg during co-administration with boceprevir.

Effects of Atorvastatin on the pharmacokinetics of co-administered medicinal products:
Digoxin: Patients taking digoxin should be monitored appropriately.
Oral contraceptive: No specific recommendation.
Phenazone: No specific recommendation.
Tipranavir and ritonavir: No specific recommendation.
Fosamprenavir: No specific recommendation.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: Atorvastatin had no effect on male or female fertility.
Pregnancy: Women of child-bearing potential should use appropriate contraceptive measures during treatment. Atorvastatin is contraindicated during pregnancy. Safety in pregnant women has not been established. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. 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.
Breast-feeding: It is unknown whether atorvastatin or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions, women taking Atorvastatin should not breast-feed their infants. Atorvastatin is contraindicated during breast-feeding.

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 reactions ranked according to the following convention: common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available 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: Hypoglycemia, weight gain, anorexia.
Psychiatric disorders:
Uncommon: Nightmare, insomnia
Nervous system disorders:
Common: Headache
Uncommon: Dizziness, paraesthesia, hypothesia, 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
Vascular disorders:
Rare: vasculitis
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 tissues disorders:

Uncommon: Urticaria, skin rash, pruritus, alopecia

Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and lichenoid drug reaction.

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

Reproductive system and breast disorders:

Very rare: Gynaecomastia

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

The following adverse events have been reported 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 ≥5.6 mmol/l, BMI>30 kg/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.

Mechanism of action: 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.

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. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. 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 pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

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

Biotransformation: Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and para-hydroxylated 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 para-hydroxylated 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. 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.

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_{0-24h} 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 foetuses. In rats, rabbits and dogs' atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal 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.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

TRUVA™ 10mg Tablet:

- Calcium Carbonate
- Microcrystalline cellulose
- Lactose monohydrate
- Hydroxypropyl Cellulose
- Croscarmellose Sodium
- Polysorbate
- Magnesium stearate
- Sheffcoat PVA White
- Red iron oxide color

TRUVA™ Tablet 20mg:

- Calcium Carbonate
- Microcrystalline cellulose
- Lactose monohydrate
- Hydroxypropyl Cellulose
- Croscarmellose Sodium
- Polysorbate
- Magnesium stearate
- Sheffcoat PVA White
- Apple Green Lake color

TRUVA™ Tablet 40mg:

- Calcium Carbonate

- Microcrystalline cellulose
- Lactose monohydrate
- Hydroxypropyl Cellulose
- Croscarmellose Sodium
- Polysorbate
- Magnesium stearate
- Sheffcoat PVA White
- Red iron oxide color

6.2. INCOMPATIBILITIES:
Not applicable.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Do not store over 30°C, and protect from heat and moisture.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
TRUVA™ 10mg Tablet: Alu/Alu blister, pack size is 10's.
TRUVA™ Tablet 20mg: Alu/Alu blister, pack size is 10's.
TRUVA™ Tablet 40mg: Alu/Alu blister, pack size is 10's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
TRUVA™ 10mg Tablet: USP Specs.
TRUVA™ Tablet 20mg: USP Specs.
TRUVA™ Tablet 40mg: USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

TRUVA™ 10mg Tablet: 036351
TRUVA™ Tablet 20mg: 100510
TRUVA™ Tablet 40mg: 100511

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

TRUVA™ 10mg Tablet: 31st December, 2004
TRUVA™ Tablet 20mg: 19th December, 2019
TRUVA™ Tablet 40mg: 19th December, 2019

10. DATE OF REVISION OF THE TEXT

ٹروا™ ٹیبلٹ

(اِیٹوروا سٹیٹن کیلشیم)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،
گرمی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔