28-07-2020

TRUVA™ Tablet
(Atorvastatin)

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

PHARMACEUTICAL FORM
Tablets

CLINICAL PARTICULARS
THERAPEUTIC INDICATIONS: Hypercholesterolemia: 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 hypercholesterolemia including familial hypercholesterolemia (heterozygous variant) or combined (mixed) hyperlipidemia (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 hypercholesterolemia 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.

POSOLOGY AND METHOD OF ADMINISTRATION: Posology: 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 individualized according to baseline LDL-C levels, the goal of therapy, and patient response. The usual starting dose is 10mg once a day. Adjust dose at intervals of 4 weeks or more. The maximum dose is 80mg once a day.
Primary hypercholesterolemia and combined (mixed) hyperlipidemia: The majority of patients are controlled with **TRUVA™** 10mg film coated tablets 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 hypercholesterolemia: Patients should be started with **TRUVA™** 10mg film coated tablets 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 atorvastatin once daily.
Homozygous familial hypercholesterolemia: Only limited data is available. The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80mg 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 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.
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 atorvastatin is not recommended in patients taking letermovir co-administered with cyclosporin.
Renal Impairment: No adjustment of dose is required.
Hepatic Impairment: Atorvastatin is contraindicated in patients with active liver disease and should be used with caution in patients with hepatic impairment.
Elderly Patients: Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.
Paediatric Patients:
Hypercholesterolemia: 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 atorvastatin is 10mg per day which may be increased to 80mg daily, according to the response and tolerability. Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more. The dose titration to 80mg daily is supported by study data in adults and by limited clinical data from studies in children with heterozygous familial hypercholesterolemia. Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

Method of Administration: For oral administration. Dose to be given all at once, at any time of day, with or without food.

CONTRAINDICATIONS: **TRUVA™** 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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Liver effects: Liver function tests should be performed before the initiation of treatment. Increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of atorvastatin is recommended. 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): The potential risk of hemorrhagic stroke should be carefully considered before initiating treatment.
Skeletal muscle effects: In rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis. Very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with some statins.
Before the treatment: 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.
- Liver disease.

In elderly (age > 70 years), the necessity of such measurement should be considered.
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 discontinue treatment if CK Levels are found to be significantly elevated (> 5 times ULN), If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin initiate at lowest dose and with close monitoring.
Concomitant treatment with other medicinal products: Risk of rhabdomyolysis is increased with medicinal products (e.g. cyclosporin, 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.
In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued only be considered under close medical supervision.
Paediatric Population: No clinically significant effect on growth and sexual maturation
Interstitial lung disease: Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.
Diabetes Mellitus: Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS: Effect of co-administered medicinal products on atorvastatin:
Concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe.
CYP3A4 inhibitors: Co-administration of potent CYP3A4 inhibitors (e.g. cyclosporin, 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.
Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil, amiodarone and fluconazole) may increase plasma concentrations of atorvastatin. Clinical monitoring is recommended. Increase risk of myopathy has been observed.
CYP3A4 inducers: Delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.
Transport inhibitors: Inhibitors of transport proteins (e.g. cyclosporin, letermovir) can increase the systemic exposure. Dose reduction and clinical monitoring for efficacy is recommended. Not recommended in patients taking letermovir co-administered with cyclosporin.
Gemfibrozil / fibric acid derivatives: The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk is increased with the concomitant use of fibric acid derivatives and atorvastatin. Patients should be appropriately monitored.
Ezetimibe: The risk of muscle related events, including rhabdomyolysis may be increased. Appropriate clinical monitoring of these patients is recommended.
Colestipol: Caution is advised, should be given alone.
Fusidic acid: If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.
Colchicine: Caution should be exercised when prescribing atorvastatin with colchicine.
Effect of atorvastatin on co-administered medicinal products:
Digoxin: 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.

210mm

120mm

Warfarin: Caution is advised in patient taking anticoagulants.
Paediatric Population: 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.

DRUG INTERACTIONS: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin:
Glecaprevir/Pibrentasvir: Co-administration with products containing glecaprevir or pibrentasvir is contraindicated.
Tipranavir/Ritonavir, Telaprevir, & Cyclosporin: Do not exceed 10mg atorvastatin daily. Clinical monitoring of these patients is recommended.
Elbasvir/Grazoprevir: The dose of atorvastatin should not exceed a daily dose of 20mg.
Lopinavir/Ritonavir & Clarithromycin: Lower maintenance doses of atorvastatin are recommended, exceeding 20mg, clinical monitoring of these patients is recommended.
Saquinavir/Ritonavir, Darunavir/Ritonavir, Itraconazole, Fosamprenavir/Ritonavir, Fosamprenavir: Lower maintenance doses of atorvastatin are recommended.
Letermovir: The dose of atorvastatin should not exceed a daily dose of 20mg.
Amlodipine, Cimetidine, Colestipol, Antacid suspension of magnesium and aluminium hydroxides, & Efavirenz, Nelfinavir: No specific recommendation.
Grapefruit Juice: Large quantities of grapefruit juice with atorvaststin is not recommended.
Rifampin & Diltiazem, Gemfibrozil, Fenofibrate, Boceprevir: Appropriate clinical monitoring of these patients is recommended.
Erythromycin: Lower dose and clinical monitoring of these patients is recommended.

FERTILITY, PREGNANCY AND LACTATION: Fertility: In animal studies atorvastatin had no effect on male or female fertility.
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. 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.
Breastfeeding: It is unknown whether atorvastatin or its metabolites are excreted in human milk. Due to the potential for serious adverse reactions, women taking atorvastatin should not breast-feed their infants. Atorvastatin is contraindicated during breast-feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Atorvastatin has negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS: The following presents the adverse reaction profile for atorvastatin;
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:* hyperglycemia. *Uncommon*: hypoglycemia, 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, tendinopathy, sometimes complicated by rupture. *Very rare:* lupus-like syndrome. *Not known:* immune mediated necrotising 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 (CK) level increased. *Uncommon:* white blood cells urine positive. Elevated serum transaminases have been reported in patients receiving atorvastatin.
Paediatric Population: The safety and tolerability profile in paediatric patients was similar to the known safety profile of atorvastatin in adult patients.
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 depending on risk factors.

OVERDOSE: Specific treatment is not available for atorvastatin overdose. Patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMICS PROPERTIES:
Therapeutic Classification: 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 hypercholesterolemia, a population that has not usually responded to lipid-lowering medicinal products. Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

PHARMACOKINETIC 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.
Distribution: Mean volume of distribution is approximately 381 L. Atorvastatin is ≥98% bound to plasma proteins.
Biotransformation: 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. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours.
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 population: Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight.
Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men. These differences were of no clinical significance, resulting in no 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 markedly increased in patients with chronic alcoholic liver disease (Child-Pugh B).

STABILITY

See expiry on the pack

AVAILABILITY

TRUVA™ 10mg tablet in a pack of 10's
TRUVA™ tablet 20mg in a pack of 10's

INSTRUCTIONS

Dosage as advised by the physician.
To be sold on the prescription of registered medical practitioner.
Keep out of reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Store in the original package in order to protect from moisture.

Full Prescribing Information available on www.samipharmapk.com

ٹروواTM ٹیبلٹ

(ایٹوروا سٹیٹن)

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 دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں
ورنہ دوا خراب ہو جائیگی۔
دوا کو نمی سے محفوظ رکھنے کے لیے اسکی اصل پیکنگ میں رکھیں۔

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210mm

120mm