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BRAND NAME:DUOPHARMA ATORVASTATIN

PRODUCT NAME
DUOPHARMA ATORVASTATIN TABLET 40MG
DUOPHARMA ATORVASTATIN TABLET 20MG

ACTIVE INGREDIENT Crystalline Atorvastatin Calcium

PRODUCT DESCRIPTION
ATORVASTATIN TABLET 40MG - White to off-white, 10 mm round, biconvex, with “40” marking on one side and plain on the other side, film-coated tablet.

ATORVASTATIN TABLET 20MG -White to off-white, 7 mm round, biconvex, with “20” marking on one side and plain on the other side, film-coated tablet.

PHARMACODYNAMICS Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA-reductase inhibitors, ATC code: C10AA05

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

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

PHARMACOKINETIC
Absorption
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (Cmax) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

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

Biotransformation
Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolised via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites 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 multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special populations
Elderly
Plasma concentrations of atorvastatin and its active metabolites are 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. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Gender
Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for Cmax and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

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

Hepatic impairment
Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in Cmax and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

SLOC1B1 polymorphism
Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see Warnings and Precaution). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown

THERAPEUTIC INDICATIONS
Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated total cholesterol , LDL-Cholesterol, apolipoprotein B and triglycerides and to increase HDL-Cholesterol in patients with primary hypercholesterolemia (heterozygous familial and non-familial hypercholesterolemia), combined (mixed) hyperlipidemia (Fredrickson Types IIa and IIb), elevated serum triglyceride levels (Fredrickson Type IV) and for patients with dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

Atorvastatin is also indicated for the reduction to total cholesterol and LDL-cholesterol in patients with homozygous familial hypercholesterolemia.

Prevention of Cardiovascular Disease
In adult patients without clinically evident coronary heart disease but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, DUOPHARMA ATORVASTATIN is indicated to :
- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking or hypertension, DUOPHARMA ATORVASTATIN is indicated to :
- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin is indicated to :
- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

Pediatric Patient (10-17 years of age)
Atorvastatin is indicated as an adjunct to diet to reduce total-C and apo B levels in boys and postmenarchal girls 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
a. LDL-C remains ≥ 190 mg/dl or
b. LDL-C remains ≥ 160 mg/dl and :

• There is a positive family history of premature cardiovascular disease or
• Two or more other CVD risk factors are present in the pediatric patient

RECOMMENDED DOSE
ROUTE OF ADMINISTRATION: ORAL
General
Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise and weight reduction in obese patients, and to treat the underlying medical problems. The patient should continue on a standard cholesterol-lowering diet during treatment with atorvastatin. The dosage range is 10mg to 80mg once daily. Doses may be given any time of the day with or without food. Starting and maintenance dosage should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2-4 weeks, and dosage adjusted accordingly

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia
The majority of patients are controlled with 10mg atorvastatin once daily. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Homozygous Familial Hypercholesterolemia
In a compassionate-use study of patients with homozygous familial hypercholesterolemia, most patients responded to 80mg atorvastatin with a greater than 15% reduction in LDL-C (18%-45%)

Heterozygous Famililal Hypercholesterolemia in Pediatric Patients (10-17 years of age)
The recommended starting dose of atorvastatin is 10mg/day; the usual dose range is 10 to 20mg orally once daily. Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more

Severe Dyslipidemias in Pediatric Patients
For patients aged 10 years and above, the recommended starting dose is 10mg atorvastatin once daily. The dose 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.

Use in Patients with Renal Insufficiency
Renal disease has no influence on plasma concentration or on LDL-C reduction with atorvastatin. Thus, no dose adjustment is required.

Use in Elderly
No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

Dosage in Patients taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protein Inhibitors
In patients taking cyclosporine or the human immunodeficiency virus (HIV) protease inhibitors (tipanivir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with atorvastatin should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary is employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with atorvastatin should be limit to 20mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with atorvastatin should be limited to 40mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed.

Use in Children (Homozygous Familial Hypercholesterolemia)
Treatment experience in a pediatric population is limited to doses of atorvastatin up to 80mg/day for one year in 8 patients with homozygous FH. No clinical or biochemical abnormalities were reported in these patients.

CONTRAINDICATION
DUOPHARMA ATORVASTATIN is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients present in this 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 (see Fertility, Pregnancy and Lactation)
- treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

WARNINGS AND PRECAUTION
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 DUOPHARMA ATORVASTATIN is recommended (see Possible Side Effects).
DUOPHARMA 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 haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see Pharmacodynamics).

Skeletal muscle effects
Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment, muscle biopsy showing necrotizing myopathy without significant inflammation, improvement with immunosuppressive agents.

Physicians considering combined therapy with atorvastatin and fibrates, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin (≥1g/day) should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Therefore, lower starting and maintenance doses of atorvastatin should also be considered when taken concomitantly with the aforementioned drugs. Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy.

Before the treatment
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions (see Interaction) and special populations including genetic subpopulations (see Pharmacokinetics)

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.

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 and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin, or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see Interaction).

Atorvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see Interaction). 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 DUOPHARMA 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 (see Possible Side Effects).

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see Possible Side Effects). Presenting features can include dyspnoea, nonproductive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes Mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

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

INTERACTION WITH OTHER MEDICAMENTS
Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see Pharmacokinetics). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see Contraindications and Warning & Precautions).

CYP3A4 inhibitors
Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatment of HCV (e.g., elbasvir/grazoprevir), and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has been 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 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 (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).

Gemfibrozil / fibric acid derivatives
The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see Warning and Precautions).

Concurrent use of fibrates may cause severe myositis and myoglobinuria.

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 *(see Warning and Precautions).*

Colchicine
Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin

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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, co-administration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Paediatric population

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.

Drug interactions

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

Co-administered medicinal product and dosing regimen	Atorvastatin	
	Dose (mg)	Clinical Recommendation#
Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7 days	10 mg OD for 7 days	Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section Contraindication).
Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	In cases where co-administration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended.
Telaprevir 750 mg q8h, 10 days	20 mg, SD	
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 4-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended
Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	
Itraconazole 200 mg OD, 4 days	40 mg SD	
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	
Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days	10 mg SD	The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing elbasvir or grazoprevir.
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	No specific recommendation.
Grapefruit Juice, 240 mL OD *	40 mg, SD	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended
Diltiazem 240 mg OD, 28 days	40 mg, SD	After initiation or following dose adjustment of diltiazem, appropriate clinical monitoring of these patients is recommended
Erythromycin 500 mg QID, 7 days	10 mg, SD	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	No specific recommendation
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 2 weeks	No specific recommendation.
Colestipol 10 g BID, 24 weeks	40 mg OD for 8 weeks	No specific recommendation.
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 17 days	10 mg OD for 15 days	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	No specific recommendation.
Rifampin 600 mg OD, 7 days (coadministered)	40 mg SD	If co-administration cannot be avoided, simultaneous coadministration of atorvastatin with rifampin is recommended, with clinical monitoring.
Rifampin 600 mg OD, 5 days (doses separated	40 mg SD	
Gemfibrozil 600 mg BID, 7 days	40 mg SD	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40 mg SD	Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir 800 mg TID, 7 days	40 mg SD	Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during coadministration with boceprevir.

& Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

See Warning and Precautions and Interaction for clinical significance.

* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold.

** Ratio based on a single sample taken 8-16 h post dose.

OD = once daily; SD = single dose; BID = twice daily; TID = three times daily; QID = four times daily.

Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products.

Atorvastatin and dosing regimen	Co-administered medicinal product	
	Medicinal product/Dose (mg)	Clinical Recommendation
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	Patients taking digoxin should be monitored appropriately.
40 mg OD for 22 days	Oral contraceptive OD, 2 months - norethindrone 1 mg - ethinyl estradiol 35 µg	No specific recommendation.
80 mg OD for 15 days	* Phenazone, 600 mg SD	No specific recommendation.
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 day	No specific recommendation.
10 mg, OD for 4 days	Fosamprenavir 1400 mg BID, 14 days	No specific recommendation.
10 mg OD for 4 days	Fosamprenavir 700 mg BID/ ritonavir 100 mg BID, 14 days	No specific recommendation.

& Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

OD = once daily; SD = single dose; BID = twice daily.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment *(see Contraindications).*

Pregnancy

DUOPHARMA ATORVASTATIN is contraindicated during pregnancy (see Contraindications). 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. Studies in animals have shown toxicity to reproduction.

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, DUOPHARMA ATORVASTATIN should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with DUOPHARMA ATORVASTATIN should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant *(see Contraindications).*

Breast-feeding

It is unknown 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 DUOPHARMA ATORVASTATIN should not breast-feed their infants (see Contraindications). Atorvastatin is contraindicated during breast-feeding *(see Contraindications).*

Fertility

In animal studies atorvastatin had no effect on male or female fertility.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES

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

SIDE EFFECTS

Following table presents the adverse reaction profile for DUOPHARMA 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: hyperglycaemia.
Uncommon: hypoglycaemia, weight gain, anorexia.

Psychiatric disorders
Uncommon: nightmare, insomnia.

Nervous system disorders
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.

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

Ear and labyrinth disorders
Uncommon: tinnitus.
Very rare: hearing loss.

Respiratory, thoracic and mediastinal disorders
Common: pharyngolaryngeal pain, epistaxis.

Gastrointestinal disorders
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.

Hepatobiliary disorders
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.

Skin and subcutaneous tissue disorders
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.
Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture.
Very rare: lupus-like syndrome.
Frequency not known: immune mediated necrotizing myopathy (see Warnings and Precautions).

Reproductive system and breast disorders
Very rare: gynecomastia.

General disorders and administration site conditions
Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.

Investigations
Common: liver function test abnormal, blood creatine kinase increased.
Uncommon: white blood cells urine positive.
As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving Atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. These elevations were dose related and were reversible in all patients.

Paediatric population
The safety and tolerability profile in paediatric patients was similar to the known safety profile of atorvastatin in adult patients.
Based on the data available, the frequency, type and severity of adverse reactions in children is similar to adults.

The following adverse events have been reported with some statins:
- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section Warning and Precautions).
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension).

There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).
Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

OVERDOSE

Specific treatment is not available for DUOPHARMA 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.

STORAGE

Store below 30°C, protected from moisture

DOSAGE FORM AND PACKAGING

Duopharma Atorvastatin Tablet 40mg
Duopharma Atorvastatin Tablet 20mg
Box of 3 x 10's tablets
Box of 10 x 10's tablets

SHELF LIFE

As indicated on the outer package.

PRODUCT REGISTRATION HOLDER

Duopharma Marketing Sdn. Bhd.
Lot No. 2,4,6,8,10, Jalan P/7, Section 13, Bangi Industrial Estate,
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MANUFACTURER

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DATE OF REVISION

March 2025

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DUOPHARMA