

For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

MODLIP-D

(Atorvastatin and Vitamin D₃ tablets)

COMPOSITION

MODLIP D 10

Each film coated tablet contains:

Atorvastatin Calcium I.P. equivalent to Atorvastatin 10 mg

Vitamin D₃ I.P. (Cholecalciferol)I.P. 1000 I.U.

Excipients q.s.

Color: Titanium Dioxide I.P.

Appropriate overages of Vitamin D₃ added to compensate loss on storage.

MODLIP D 20

Each film coated tablet contains:

Atorvastatin Calcium I.P. equivalent to Atorvastatin 20 mg

Vitamin D₃ I.P. (Cholecalciferol)I.P.1000 I.U.

Excipients q.s.

Color: Titanium Dioxide I.P.

Appropriate overages of Vitamin D₃ added to compensate loss on storage.

DOSAGE FORM

Film coated tablet

INDICATION

Hypercholesterolaemia

It 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. This drug 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

DOSE AND METHOD OF ADMINISTRATION

This fixed dose combination of atorvastatin 10 mg + vitamin D₃ 1000IU should be taken once daily. The maximum dose for atorvastatin is 80 mg and 4000 IU for vitamin D₃ once a day.

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin.

The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.

Patients with renal impairment

Vitamin D₃ should not be used in patients with severe renal impairment.

Patients with hepatic impairment

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

Use in the elderly

Efficacy and safety of atorvastatin in patients older than 70 using recommended doses are similar to those seen in the general population.

Method of administration

Each daily dose of is given all at once and may be given at any time of day with or without food.

USE IN SPECIAL POPULATIONS

Atorvastatin

Women of childbearing potential

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

Pregnancy

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

Maternal treatment with atorvastatin may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

For these reasons, atorvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with atorastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant.

Breastfeeding

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

Fertility

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

Vitamin D₃

Fertility

There are no data on the effect of vitamin D₃ on fertility. However, normal endogenous levels of vitamin D are not expected to have any adverse effects on fertility.

Pregnancy

Vitamin D₃ should be used during pregnancy, only in the case of a vitamin D deficiency. Vitamin D₃ is not recommended during pregnancy in patients without a vitamin D deficiency as the daily intake should not exceed 600 IU vitamin D. Studies in animals have shown reproductive toxicity of high doses of vitamin D. There are no indications that vitamin D at therapeutic doses is teratogenic in humans.

Breast-feeding

Vitamin-D can be used during breast-feeding. Vitamin D₃ passes into breast milk. This should be considered when giving additional vitamin D to the child.

CONTRAINDICATIONS

Atorvastatin is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients of this medicinal product
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures

Vitamin D₃ is contraindicated in:

- Diseases and/or conditions resulting in hypercalcaemia or hypercalciuria
- Nephrolithiasis
- Nephrocalcinosis
- Hypervitaminosis D
- Hypersensitivity to the active substance or to any of the excipients

WARNINGS AND PRECAUTIONS

Atorvastatin

Liver effects

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

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment.

Skeletal muscle effects

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.

Before the treatment

Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions and special populations including genetic subpopulations

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

Creatine kinase measurement

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.

Whilst on treatment

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to $\leq 5 \times$ ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Atorvastatin must be discontinued if clinically significant elevation of CK levels (> 10 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. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, boceprevir, erythromycin, niacin, ezetimibe, telaprevir, or the combination of tipranavir/ritonavir. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

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.

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.

The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy.

Paediatric use

Developmental safety in the paediatric population has not been established.

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 6.9 mmol/L, BMI > 30 kg/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Vitamin D₃

Vitamin D₃ should be prescribed with caution to patients suffering from sarcoidosis due to risk of increased metabolism of vitamin D into its active form. These patients should be monitored with regard to the calcium content in serum and urine.

During long-term treatment, serum calcium levels should be followed and renal function should be monitored through measurements of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics and in patients with a high tendency to calculus formation. In case of hypercalciuria (exceeding 300 mg (7.5 mmol)/24 hours) or signs of impaired renal function the dose should be reduced or the treatment discontinued.

Vitamin D₃ should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of colecalciferol is not metabolised normally and other forms of vitamin D should be used.

The content of vitamin D (800 IU) should be considered when prescribing other medicinal products containing vitamin D. Additional doses of vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

Vitamin D₃ contain sucrose and isomalt. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Vitamin D₃ is not recommended in children.

DRUG INTERACTIONS

Atorvastatin

Effect of co-administered medicinal products on atorvastatin

Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivatives and ezetimibe.

CYP3A4 inhibitors

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

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

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

Gemfibrozil / fibric acid derivatives

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

Ezetimibe

The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.

Colestipol

Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) 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

Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

Colchicine

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

Effect of atorvastatin on co-administered medicinal products

Digoxin

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.

Oral contraceptives

Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

Warfarin

In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions 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 in should be taken into account for the paediatric population.

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

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC ^{&}	Clinical Recommendation
Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	↑ 9.4 fold	In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended
Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.9 fold	
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	↑ 8.7 fold	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	↑ 5.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	↑ 4.4 fold	
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 4-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	↑ 3.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	↑ 3.3 fold	
Itraconazole 200 mg OD, 4 days	40 mg SD	↑ 3.3 fold	
Fosamprenavir 700 mg BID/	10 mg	↑ 2.5	

Ritonavir 100 mg BID, 14 days	OD for 4 days	fold	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	↑ 2.3 fold	
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	↑ 1.7 fold [^]	No specific recommendation
Grapefruit Juice, 240 mL OD *	40 mg, SD	↑ 37%	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	↑ 51%	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33% [^]	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	↑ 18%	No specific recommendation.
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 2 weeks	↓ less than 1% [^]	No specific recommendation.
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks	10 mg OD for 4 weeks	↓ 35% [^]	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	↓ 41%	No specific recommendation.
Rifampin 600 mg OD, 7 days (co-administered)	40 mg SD	↑ 30%	If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.
Rifampin 600 mg OD, 5 days (doses separated)	40 mg SD	↓ 80%	
Gemfibrozil 600 mg BID, 7 days	40mg SD	↑ 35%	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40mg SD	↑ 3%	Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir 800 mg TID, 7 days	40mg SD	↑ 2.3 fold	Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir.

&Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change).

Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

*Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolized 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).

^ Total atorvastatin equivalent activity

Increase is indicated as “↑”, decrease as “↓”

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

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

Atorvastatin and dosing regimen	Co-administered medicinal product		
	Medicinal product/Dose (mg)	Change in AUC ^{&}	Clinical Recommendation
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	↑ 15%	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	↑ 28% ↑ 19%	No specific recommendation.
80 mg OD for 15 days	* Phenazone, 600 mg SD	↑ 3%	No specific recommendation
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No specific recommendation
10 mg, OD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	No specific recommendation
10 mg OD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No specific recommendation

&Data given as % change represent % difference relative to medicinal product alone (i.e., 0% = no change)

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

Increase is indicated as “↑”, decrease as “↓”

OD = once daily; SD = single dose

Vitamin D₃

Thiazide diuretics reduce the urinary excretion of calcium. Due to the increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Concomitant use of phenytoin or barbiturates may reduce the effect of vitamin D since the metabolism increases.

Excessive dosing of vitamin D can induce hypercalcaemia, which may increase the risk of digitalis toxicity and serious arrhythmias due to the additive inotropic effects. The electrocardiogram (ECG) and serum calcium levels of patients should be closely monitored.

Glucocorticoid steroids may increase vitamin D metabolism and elimination. During concomitant use, it may be necessary to increase the dose of vitamin D₃ tablets.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.

UNDESIRABLE EFFECTS

Atorvastatin

Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for atorvastatin.

Estimated frequencies of reactions are ranked according to the following convention: common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($\leq 1/10,000$), 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: 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.

Not known: immune-mediated necrotizing myopathy.

Reproductive system and breast disorders

Very rare: gynecomastia.

General disorders and administration site conditions

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

Investigations

Common: liver function test abnormal, blood creatine kinase increased.

Uncommon: white blood cells urine positive.

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving Atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on Atorvastatin. These elevations were dose related and were reversible in all patients.

Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on Atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% Atorvastatin treated patients.

Paediatric Population

The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.

Nervous system disorders

Common: Headache

Gastrointestinal disorders

Common: Abdominal pain

Investigations

Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.

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).

Vitamin D₃

Adverse reactions frequencies are defined as: uncommon ($\geq 1/1,000$, < 1/100), rare ($\geq 1/10,000$, < 1/1,000) or not known (cannot be estimated from the available data).

Immune system disorders

Not known (cannot be estimated from the available data): Hypersensitivity reactions such as angio-oedema or laryngeal oedema.

Metabolism and nutrition disorders

Uncommon: Hypercalcaemia and hypercalciuria.

Skin and subcutaneous disorders

Rare: Pruritus, rash and urticaria.

OVERDOSE

Atorvastatin

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.

Vitamin D₃

Overdose can lead to hyper-vitaminosis D. An excess of vitamin D causes abnormally high levels of calcium in the blood, which can eventually severely damage the soft tissues, and kidneys. Tolerable upper intake level for vitamin D₃ (coleciferol) is set at 4000 IU (100 µg) per day. Vitamin D₃ should not be confused with its active metabolites.

Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death. Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification.

Treatment of hypercalcaemia: The treatment with vitamin D must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, and cardiac glycosides must also be discontinued. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should be considered. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Atorvastatin

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 catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

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

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

Atorvastatin has been shown to reduce concentrations of total-C (30% - 46%), LDL-C (41% - 61%), apolipoprotein B (34% - 50%), and triglycerides (14% - 33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

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

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. 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 $\geq 98\%$ bound to plasma proteins.

Biotransformation

Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Special populations

Elderly

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

Paediatric

In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage ≥ 2 (N=24) paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C ≥ 4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were 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 C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Patients with renal impairment

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

Patients with hepatic impairment

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

SLCO1B1 polymorphism

Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

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 fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

Vitamin D₃

Vitamin D, in addition to increasing intestinal calcium absorption, reducing parathyroid hormone levels and improving the amount and quality of bone, has a beneficial vascular effect. Vitamin D deficiency has been associated with peripheral arterial disease and myocardial infarction. Vitamin D deficiency may increase the risk of cardiovascular disease through three possible mechanisms. Firstly, in vitro studies have reported that vitamin D may cause an imbalance between anti-inflammatory and proinflammatory cytokines, reducing NF- κ B activity, increasing IL-10 production, and reducing levels of IL-6, IL-1, interferon γ , and TNF α . Secondly, endothelial cells have receptors for vitamin D whose stimulation inhibits cell proliferation. Thirdly, the association between hypertension and vitamin D deficit is mediated by activation of the renin-angiotensin aldosterone system. High calcitriol levels reduce plasma renin activity, leading to reduced plasma angiotensin II concentrations. This modulation of the renin-angiotensin aldosterone system, in addition to reducing blood pressure, reduces inflammation of the vascular endothelium, thus limiting atherosclerosis progression.

Absorption: Vitamin D is easily absorbed in the small intestine. Distribution and metabolism: Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. Cholecalciferol is converted in the liver by hydroxylation to 25-hydroxy - Cholecalciferol. It is then further converted in the kidneys to 1,25-dihydroxyCholecalciferol. 1,25-dihydroxyCholecalciferol is the active metabolite responsible for increasing calcium absorption. Vitamin D, which is not metabolised, is stored in adipose and muscle tissues. Elimination: Vitamin D is excreted in faeces and urine.

EXPIRY DATE

Do not use later than the date of expiry.

PACKAGING INFORMATION

Modlip D is available as blister of 10 tablets.

STORAGE AND HANDLING INSTRUCTIONS

Store at a temperature not exceeding 30°C, protected from light and moisture. Keep out of the reach of children.

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