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

MODLIP EZ

(Atorvastatin and Ezetimibe Tablets 10mg+10mg)

COMPOSITION

MODLIP EZ

Each film coated tablet contains:
Atorvastatin Calcium I.P. equivalent to
Atorvastatin 10 mg
Ezetimibe 10 mg
Colours: Lake of Sunset Yellow and Titanium Dioxide I.P.
Excipients q.s.

DOSAGE FORM

Film coated tablet

INDICATION

MODLIP EZ is indicated for the treatment of patients with primary hypercholesterolemia.

DOSE AND METHOD OF ADMINISTRATION

Adult dose: The recommended starting dose is 1 tablet (Ezetimibe 10 mg and Atorvastatin 10 mg) once daily. The drug can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses should be individualized according to patient characteristics such as goal of therapy and response. The patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with MODLIP EZ.

CONTRAINDICATIONS

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.
- When Ezetimibe is co-administered with a statin, please refer to the SPC for that particular medicinal product.
- Therapy with Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation.
- Ezetimibe co-administered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 ≤ 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. 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 derivates, 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>30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Ezetimibe
When Ezetimibe is co-administered with a statin, please refer to the SPC for that particular medicinal product.
Liver Enzymes
In controlled co-administration trials in patients receiving Ezetimibe with a statin, consecutive transaminase elevations (≥ 3 X the upper limit of normal [ULN]) have been observed. When Ezetimibe is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin.
In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with coronary heart disease and ACS event history were randomised to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin.
In a controlled clinical study in which over 9000 patients with chronic kidney disease were randomised to receive Ezetimibe 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median follow-up period of 4.9 years), the incidence of consecutive

elevations of transaminases (>3 X ULN) was 0.7% for Ezetimibe combined with simvastatin and 0.6% for placebo.

Skeletal Muscle

In post-marketing experience with Ezetimibe , cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with Ezetimibe . However, rhabdomyolysis has been reported very rarely with Ezetimibe monotherapy and very rarely with the addition of Ezetimibe to other agents known to be associated with increased risk of rhabdomyolysis. If myopathy is suspected based on muscle symptoms or is confirmed by a creatine phosphokinase (CPK) level >10 times the ULN, Ezetimibe , any statin, and any of these other agents that the patient is taking concomitantly should be immediately discontinued. All patients starting therapy with Ezetimibe should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness.

In IMPROVE-IT, 18,144 patients with coronary heart disease and ACS event history were randomised to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 times ULN and <10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury. In a clinical trial in which over 9000 patients with chronic kidney disease were randomised to receive Ezetimibe 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median follow-up 4.9 years), the incidence of myopathy/rhabdomyolysis was 0.2% for Ezetimibe combined with simvastatin and 0.1% for placebo

Patients with hepatic impairment

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, Ezetimibe is not recommended

Paediatric population

Efficacy and safety of Ezetimibe in patients 6 to10 years of age with heterozygous familial or non-familial hypercholesterolemia have been evaluated in a 12-week placebo-controlled clinical trial. Effects of ezetimibe for treatment periods > 12 weeks have not been studied in this age group

Ezetimibe has not been studied in patients younger than 6 years of age.

Efficacy and safety of Ezetimibe co-administered with simvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys (Tanner stage II or above) and in girls who were at least one year post-menarche.

In this limited controlled study, there was generally no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. However, the effects of ezetimibe for a treatment period > 33 weeks on growth and sexual maturation have not been studied.

The safety and efficacy of Ezetimibe co-administered with doses of simvastatin above 40mg daily have not been studied in paediatric patients 10 to 17 years of age.

The safety and efficacy of Ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10 years of age.
The long-term efficacy of therapy with Ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates

The safety and efficacy of Ezetimibe administered with fibrates have not been established.
If cholelithiasis is suspected in a patient receiving Ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued.

Ciclosporin

Caution should be exercised when initiating Ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe and ciclosporin.

Anticoagulants

If Ezetimibe is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

DRUG-INTERECTION

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 derivates and ezetimibe.

CYP3A4 inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole 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/ Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	↑ 2.5 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

FERTILITY, PREGNANCY AND LACTATION

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.

Ezetimibe
Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation. please refer to the SPC for that particular statin.
Pregnancy
Ezetimibe should be given to pregnant women only if clearly necessary. No clinical data are available on the use of Ezetimibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development.
Lactation
Ezetimibe should not be used during lactation. Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.
Fertility
No clinical trial data are available on the effects of ezetimibe on human fertility. Ezetimibe had no effect on the fertility of male or female rats.

UNDESIRABLE EFFECTS
Atorvastatin
In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

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 (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (≤ 1/10,000), not known (cannot be estimated from the available data).

Infections and infestations
Common: nasopharyngitis.

Blood and lymphatic system disorders
Rare: thrombocytopenia.

Immune system disorders
Common: allergic reactions.
Very rare: anaphylaxis.

Metabolism and nutrition disorders
Common: hyperglycaemia.
Uncommon: 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>30kg/m^2, raised triglycerides, history of hypertension).

Ezetimibe

Tabulated list of adverse reactions (clinical studies and post-marketing experience)

In clinical studies of up to 112 weeks duration, Ezetimibe 10 mg daily was administered alone in 2396 patients, with a statin in 11,308 patients or with fenofibrate in 185 patients. Adverse reactions were usually mild and transient. The overall incidence of side effects was similar between Ezetimibe and placebo. Similarly, the discontinuation rate due to adverse experiences was comparable between Ezetimibe and placebo.

Ezetimibe administered alone or co-administered with a statin:

The following adverse reactions were observed in patients treated with Ezetimibe (N=2396) and at a greater incidence than placebo (N=1159) or in patients treated with Ezetimibe coadministered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9361). Post-marketing Adverse reactions were derived from reports containing Ezetimibe either administered alone or with a statin.

Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data)

Ezetimibe monotherapy		
System organ class	**Adverse reactions**	**Frequency**
Investigations	ALT and/or AST increased; blood CPK increased; gamma-glutamyltransferase increased; liver function test abnormal	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	cough	Uncommon
Gastrointestinal Disorders	abdominal pain; diarrhoea; flatulence	Common
	dyspepsia; gastrooesophageal reflux disease; nausea	Uncommon
Musculoskeletal And Connective Tissue Disorders	arthralgia; muscle spasms; neck pain	Uncommon
Metabolism and Nutrition Disorders	decreased appetite	Uncommon
Vascular Disorders	hot flush; hypertension	Uncommon
General Disorders And Administration Site Condition	fatigue	Common
	chest pain, pain	Uncommon

Additional adverse reactions with Ezetimibe co-administered with a statin		
System organ class	**Adverse reactions**	**Frequency**
Investigations	ALT and/or AST increased	Common
Nervous System Disorders	headache	Common
	paraesthesia	Uncommon
Gastrointestinal Disorders	dry mouth; gastritis	Uncommon
Skin And Subcutaneous Tissue Disorders	pruritus; rash; urticaria	Uncommon
Musculoskeletal And Connective Tissue Disorders	myalgia	Common
	back pain; muscular weakness; pain in extremity	Uncommon
General Disorders And Administration Site Condition	asthenia; oedema peripheral	Uncommon
Post-marketing Experience (with or without a statin)		
System organ class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	thrombocytopaenia	Not known
Nervous system disorders:	dizziness; paraesthesia	Not known
Respiratory, thoracic and mediastinal disorders	dyspnoea	Not known
Gastrointestinal disorders	pancreatitis; constipation	Not known
Skin and subcutaneous tissue disorders	erythema multiforme	Not known
Musculoskeletal and connective tissue disorder	myalgia; myopathy/rhabdomyolysis	Not known
General disorders and administration site conditions	asthenia	Not known
Immune system disorders	hypersensitivity, including rash, urticaria, anaphylaxis and angio-oedema	Not known
Hepatobiliary disorders	hepatitis; cholelithiasis; cholecystitis	Not known
Psychiatric disorders	depression	Not known

Ezetimibe co-administered with fenofibrate

Gastrointestinal disorders: abdominal pain (common)

In a multicentre, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidaemia, 625 patients were treated for up to 12 weeks and 576 patients for up to 1 year. In this study, 172 patients treated with Ezetimibe and fenofibrate completed 12 weeks of therapy, and 230 patients treated with Ezetimibe and fenofibrate (including 109 who received Ezetimibe alone for the first 12 weeks) completed 1 year of therapy. This study was not designed to

compare treatment groups for infrequent events. Incidence rates (95 % CI) for clinically important elevations (> 3 X ULN, consecutive) in serum transaminases were 4.5 % (1.9, 8.8) and 2.7 % (1.2, 5.4) for fenofibrate monotherapy and Ezetimibe co-administered with fenofibrate, respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6 % (0.0, 3.1) and 1.7 % (0.6, 4.0) for fenofibrate monotherapy and Ezetimibe co-administered with fenofibrate, respectively.

Paediatric (6 to 17 years of age) Patients

In a study involving paediatric (6 to 10 years of age) patients with heterozygous familial or non-familial hypercholesterolaemia (n=138), elevations of ALT and/or AST (≥ 3X ULN, consecutive) were observed in 1.1% (1 patient) of the ezetimibe patients compared to 0% in the placebo group. There were no elevations of CPK (≥ 10X ULN). No cases of myopathy were reported.

In a separate study involving adolescent (10 to 17 years of age) patients with heterozygous familial hypercholesterolaemia (n=248), elevations of ALT and/or AST (≥ 3X ULN, consecutive) were observed in 3% (4 patients) of the ezetimibe/simvastatin patients compared to 2% (2 patients) in the simvastatin monotherapy group; these figures were respectively 2% (2 patients) and 0% for elevation of CPK (≥ 10X ULN). No cases of myopathy were reported.

These trials were not suited for comparison of rare adverse drug reactions.

Patients with Coronary Heart Disease and ACS Event History

In the IMPROVE-IT study, involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n=9067; of whom 6% were uptitrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n=9077; of whom 27% were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6.0 years. Discontinuation rates due to adverse experiences were 10.6% for patients treated with ezetimibe/simvastatin and 10.1% for patients treated with simvastatin. The incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 times ULN and <10 times ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin. Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to ezetimibe/simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalisations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.

Patients with Chronic Kidney Disease

In the Study of Heart and Renal Protection (SHARP) , involving over 9000 patients treated with a fixed dose combination of Ezetimibe 10 mg with simvastatin 20 mg daily (n=4650) or placebo (n=4620), the safety profiles were comparable during a median follow-up period of 4.9 years. In this trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse events were comparable (10.4% in patients treated with Ezetimibe combined with simvastatin, 9.8% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0.2% in patients treated with Ezetimibe combined with simvastatin and 0.1% in patients treated with placebo. Consecutive elevations of transaminases

(> 3X ULN) occurred in 0.7% of patients treated with Ezetimibe combined with simvastatin compared with 0.6% of patients treated with placebo. In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4% for Ezetimibe combined with simvastatin, 9.5% for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

Laboratory values:

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was similar between Ezetimibe (0.5 %) and placebo (0.3 %). In co-administration trials, the incidence was 1.3 % for patients treated with Ezetimibe co-administered with a statin and 0.4 % for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

In clinical trials, CPK >10 X ULN was reported for 4 of 1674 (0.2 %) patients administered Ezetimibe alone vs 1 of 786 (0.1 %) patients administered placebo, and for 1 of 917 (0.1 %) patients co-administered Ezetimibe and a statin vs 4 of 929 (0.4 %) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with Ezetimibe compared with the relevant control arm (placebo or statin alone)

OVERDOSE

Atorvasatin

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.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days, was generally well tolerated. In animals, no toxicity was observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 mg/kg in dogs.

A few cases of overdosage with Ezetimibe have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

PHARMACODYNAMIC 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 ≥ 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).

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. 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.

Ezetimibe

Pharmacotherapeutic group: Other lipid modifying agents, ATC code: C10A X09

Mechanism of action

Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. In a 2-week clinical study in 18 hypercholesterolaemic patients, Ezetimibe inhibited intestinal cholesterol absorption by 54 %, compared with placebo.

Pharmacodynamic effects

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [^{14}C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or fat soluble vitamins A and D.

Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

Administration of Ezetimibe with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

Clinical efficacy and safety

In controlled clinical studies, Ezetimibe either as monotherapy or co-administered with a statin significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG) and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

Primary Hypercholesterolaemia

In a double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/l [100 to 160 mg/dl], depending on baseline characteristics) were randomised to receive either Ezetimibe 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82 %), significantly more patients randomised to Ezetimibe achieved their LDL-C goal at study endpoint compared to patients randomised to placebo, 72 % and 19 %, respectively. The corresponding LDL-C reductions were significantly different (25 % and 4 % for Ezetimibe versus placebo, respectively). In addition, Ezetimibe, added to on-going statin therapy, significantly decreased total-C, Apo B, TG and increased HDL-C, compared with placebo. Ezetimibe or placebo added to statin therapy reduced median C-reactive protein by 10 % or 0 % from baseline, respectively.

In two, double-blind, randomised placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolaemia, Ezetimibe 10 mg significantly lowered total-C (13 %), LDL-C (19 %), Apo B (14 %), and TG (8 %) and increased HDL-C (3 %) compared to placebo. In addition, Ezetimibe had no effect on the plasma concentrations of fat-soluble vitamins A, D, and E, no effect on prothrombin time, and, like other lipid lowering agents, did not impair adrenocortical steroid hormone production.

In a multicenter, double-blind, controlled clinical study (ENHANCE), 720 patients with heterozygous familial hypercholesterolemia were randomised to receive ezetimibe 10 mg in

combination with simvastatin 80 mg (n=357) or simvastatin 80 mg (n=363) for 2 years. The primary objective of the study was to investigate the effect of the ezetimibe/simvastatin combination therapy on carotid artery intima-media thickness (IMT) compared to simvastatin monotherapy. The impact of this surrogate marker on cardiovascular morbidity and mortality is still not demonstrated.
The primary endpoint, the change in the mean IMT of all six carotid segments, did not differ significantly (p= 0.29) between the two treatment groups as measured by B-mode ultrasound. With ezetimibe 10 mg in combination with simvastatin 80 mg or simvastatin 80 mg alone, intima-medial thickening increased by 0.0111 mm and 0.0058 mm, respectively, over the study's 2 year duration (baseline mean carotid IMT 0.68 mm and 0.69 mm respectively.
Ezetimibe 10 mg in combination with simvastatin 80 mg lowered LDL-C, total-C, Apo B, and TG significantly more than simvastatin 80 mg. The percent increase in HDL-C was similar for the two treatment groups. The adverse reactions reported for ezetimibe 10 mg in combination with simvastatin 80 mg were consistent with its known safety profile.
Paediatric population
In a multicentre, double-blind, controlled study, 138 patients (59 boys and 79 girls), 6 to 10 years of age (mean age 8.3 years) with heterozygous familial or non-familial hypercholesterolaemia (HeFH) with baseline LDL-C levels between 3.74 and 9.92 mmol/l were randomised to either Ezetimibe 10 mg or placebo for 12 weeks.
At week 12, Ezetimibe significantly reduced total-C (-21% vs. 0%), LDL-C (-28% vs. -1%), Apo-B (-22% vs. -1%), and non-HDL-C (-26% vs. 0%) compared to placebo. Results for the two treatment groups were similar for TG and HDL-C (-6% vs. +8%, and +2% vs. +1%, respectively).
In a multicentre, double-blind, controlled study, 142 boys (Tanner stage II and above) and 106 postmenarchal girls, 10 to 17 years of age (mean age 14.2 years) with heterozygous familial hypercholesterolaemia (HeFH) with baseline LDL-C levels between 4.1 and 10.4 mmol/l were randomised to either Ezetimibe 10 mg co-administered with simvastatin (10, 20 or 40 mg) or simvastatin (10, 20 or 40 mg) alone for 6 weeks, co-administered Ezetimibe and 40 mg simvastatin or 40 mg simvastatin alone for the next 27 weeks, and open-label co-administered Ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter.
At Week 6, Ezetimibe co-administered with simvastatin (all doses) significantly reduced total-C (38 % vs 26 %), LDL-C (49 % vs 34 %), Apo B (39 % vs 27 %), and non-HDL-C (47 % vs 33 %) compared to simvastatin (all doses) alone. Results for the two treatment groups were similar for TG and HDL-C (-17 % vs -12 % and +7 % vs +6 %, respectively). At Week 33, results were consistent with those at Week 6 and significantly more patients receiving Ezetimibe and 40 mg simvastatin (62 %) attained the NCEP AAP ideal goal (< 2.8 mmol/L [110 mg/dL]) for LDL-C compared to those receiving 40 mg simvastatin (25 %). At Week 53, the end of the open label extension, the effects on lipid parameters were maintained.
The safety and efficacy of Ezetimibe co-administered with doses of simvastatin above 40 mg daily have not been studied in paediatric patients 10 to 17 years of age. The safety and efficacy of Ezetimibe co-administered with simvastatin have not been studied in paediatric patients < 10 years of age.
The long-term efficacy of therapy with Ezetimibe in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Prevention of Cardiovascular Events

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a multicenter, randomised, double-blind, active-control study of 18,144 patients enrolled within 10 days of hospitalisation for acute coronary syndrome (ACS; either acute myocardial infarction [MI] or unstable angina [UA]). Patients had an LDL-C ≤125 mg/dL (≤3.2 mmol/L) at the time of presentation with ACS if they had not been taking lipid-lowering therapy, or ≤100 mg/dL (≤2.6 mmol/L) if they had been receiving lipid-lowering therapy. All patients were randomised in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg (n=9067) or simvastatin 40 mg (n=9077) and followed for a median of 6.0 years.

Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 80 mg/dL (2.1 mmol/L) for those on lipid-lowering therapy (n=6390) and 101 mg/dL (2.6 mmol/L) for those not on previous lipid-lowering therapy (n=11594). Prior to the hospitalisation for the qualifying ACS event, 34% of the patients were on statin therapy. At one year, the average LDL-C for patients continuing on therapy was 53.2 mg/dL (1.4 mmol/L) for the ezetimibe/simvastatin group and 69.9 mg/dL (1.8 mmol/L) for the simvastatin monotherapy group. Lipid values were generally obtained for patients who remained on study therapy.

The primary endpoint was a composite consisting of cardiovascular death, major coronary events (MCE; defined as non-fatal myocardial infarction, documented unstable angina that required hospitalisation, or any coronary revascularisation procedure occurring at least 30 days after randomised treatment assignment) and non-fatal stroke. The study demonstrated that treatment with ezetimibe when added to simvastatin provided incremental benefit in reducing the primary composite endpoint of cardiovascular death, MCE, and non-fatal stroke compared with simvastatin alone (relative risk reduction of 6.4%, p=0.016). The primary endpoint occurred in 2572 of 9067 patients (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and 2742 of 9077 patients (7-year KM rate 34.67%) in the simvastatin alone group. (See Figure 1 and Table 1.) This incremental benefit is expected to be similar with coadministration of other statins shown to be effective in reducing the risk of cardiovascular events. Total mortality was unchanged in this high risk group (see Table 1).

There was an overall benefit for all strokes; however there was a small non-significant increase in haemorrhagic stroke in the ezetimibe-simvastatin group compared with simvastatin alone (see Table 1). The risk of haemorrhagic stroke for ezetimibe coadministered with higher potency statins in long-term outcome studies has not been evaluated.

The treatment effect of ezetimibe/simvastatin was generally consistent with the overall results across many subgroups, including sex, age, race, medical history of diabetes mellitus, baseline lipid levels, prior statin therapy, prior stroke, and hypertension.

Figure 1: Effect of Ezetimibe/Simvastatin on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

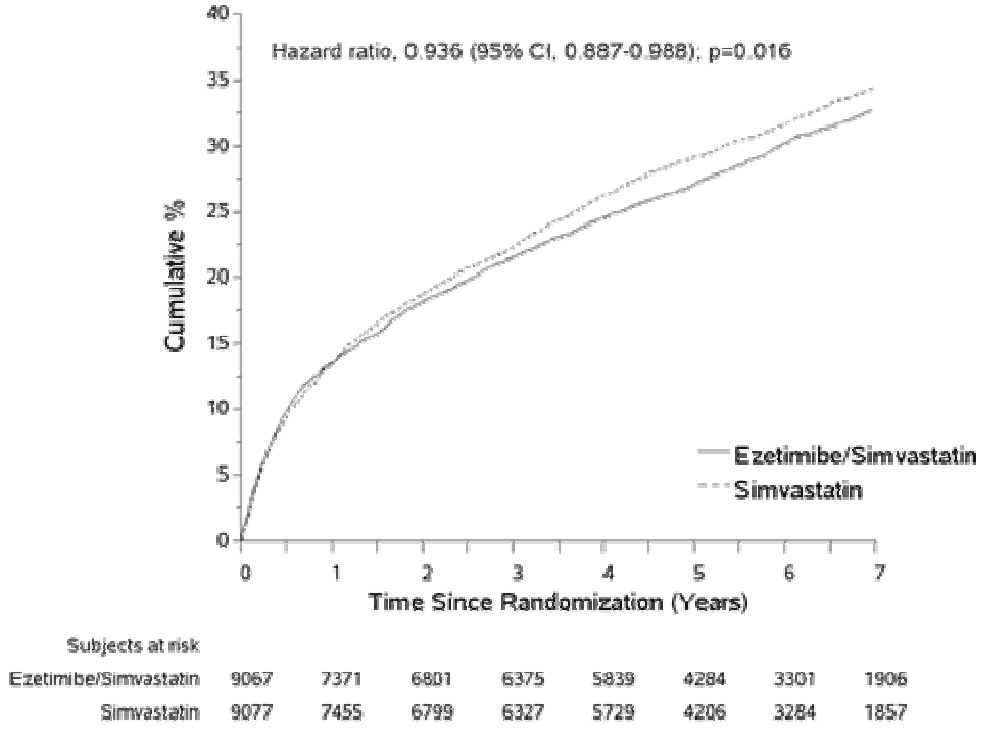

Table 1
Major Cardiovascular Events by Treatment Group in All Randomised Patients in IMPROVE-IT

Outcome	**Ezetimibe/Simvastatin 10/40 mg[a] (N=9067)**		**Simvastatin 40 mg[b] (N=9077)**		**Hazard Ratio (95% CI)**	**p-value**
	n	K-M %[c]	n	K-M %[c]		
Primary Composite Efficacy Endpoint						
(CV death, Major Coronary Events and non-fatal stroke)	2572	32.72%	2742	34.67%	0.936 (0.887, 0.988)	0.016
Secondary Composite Efficacy Endpoints						
CHD death, nonfatal MI, urgent coronary revascularisation after 30 days	1322	17.52%	1448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3089	38.65%	3246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, non-fatal MI, unstable angina requiring	2716	34.49%	2869	36.20%	0.945 (0.897, 0.996)	0.035

hospitalisation, any revascularisation, non-fatal stroke						
Components of Primary Composite Endpoint and Select Efficacy Endpoints (first occurrences of specified event at any time)						
Cardiovascular death	537	6.89%	538	6.84%	1.000 (0.887, 1.127)	0.997
Major Coronary Event:						
Non-fatal MI	945	12.77%	1083	14.41%	0.871 (0.798, 0.950)	0.002
Unstable angina requiring hospitalisation	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618
Coronary revascularisation after 30 days	1690	21.84%	1793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010
All MI (fatal and non-fatal)	977	13.13%	1118	14.82%	0.872 (0.800, 0.950)	0.002
All stroke (fatal and non-fatal)	296	4.16%	345	4.77%	0.857 (0.734, 1.001)	0.052
Non-hemorrhagic stroke [d]	242	3.48%	305	4.23%	0.793 (0.670, 0.939)	0.007
Hemorrhagic stroke	59	0.77%	43	0.59%	1.377 (0.930, 2.040)	0.110
Death from any cause	1215	15.36%	1231	15.28%	0.989 (0.914, 1.070)	0.782

[a] 6% were uptitrated to ezetimibe/simvastatin 10/80 mg.
[b] 27% were uptitrated to simvastatin 80 mg.
[c] Kaplan-Meier estimate at 7 years.
[d] includes ischemic stroke or stroke of undetermined type.

Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)

The Study of Heart and Renal Protection (SHARP) was a multi-national, randomised, placebo-controlled, double-blind study conducted in 9438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. A total of 4650 patients were allocated to a fixed dose combination of Ezetimibe 10 mg with simvastatin 20 mg and 4620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 and 63 % were male, 72 % Caucasian, 23 % diabetic and, for those not on dialysis, the mean estimated glomerular filtration rate (eGFR) was 26.5 ml/min/1.73 m^2. There were no lipid entry criteria. Mean LDL-C at baseline was 108

mg/dL. After one year, including patients no longer taking study medication, LDL-C was reduced 26 % relative to placebo by simvastatin 20 mg alone and 38 % by Ezetimibe 10 mg combined with simvastatin 20 mg.

The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as nonfatal MI or cardiac death, stroke, or any revascularisation procedure) in only those patients initially randomised to the Ezetimibe combined with simvastatin (n=4193) or placebo (n=4191) groups. Secondary analyses included the same composite analyzed for the full cohort randomised (at study baseline or at year 1) to Ezetimibe combined with simvastatin (n=4650) or placebo (n=4620) as well as the components of this composite.

The primary endpoint analysis showed that Ezetimibe combined with simvastatin significantly reduced the risk of major vascular events (749 patients with events in the placebo group vs. 639 in the Ezetimibe combined with simvastatin group) with a relative risk reduction of 16 % (p=0.001).

Nevertheless, this study design did not allow for a separate contribution of the monocomponent ezetimibe to efficacy to significantly reduce the risk of major vascular events in patients with CKD.

The individual components of MVE in all randomised patients are presented in Table 2. Ezetimibe combined with simvastatin significantly reduced the risk of stroke and any revascularisation, with non-significant numerical differences favouring Ezetimibe combined with simvastatin for nonfatal MI and cardiac death.

Table 2

Major Vascular Events by Treatment Group in all randomised patients in SHARP[a]

Outcome	Ezetimibe 10 mg combined with simvastatin 20 mg (N=4650)	Placebo (N=4620)	Risk Ratio (95% CI)	P-value
Major Vascular Events	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.001
Nonfatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-hemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Hemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularisation	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.004
Major Atherosclerotic Events (MAE)[b]	526 (11.3%)	619 (13.4%)	0.83 (0.74-0.94)	0.002

[a]Intention-to-treat analysis on all SHARP patients randomised to Ezetimibe combined with simvstatin or placebo either at baseline or year 1

[b] MAE; defined as the composite of nonfatal myocardial infarction, coronary death, non-hemorrhagic stroke, or any revascularisation

The absolute reduction in LDL cholesterol achieved with Ezetimibe combined with simvastatin was lower among patients with a lower baseline LDL-C (<2.5 mmol/l) and patients on dialysis at

baseline than the other patients, and the corresponding risk reductions in these two groups were attenuated.

Homozygous Familial Hypercholesterolaemia (HoFH)

A double-blind, randomised, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, who were receiving atorvastatin or simvastatin (40 mg) with or without concomitant LDL apheresis. Ezetimibe co-administered with atorvastatin (40 or 80 mg) or simvastatin (40 or 80 mg), significantly reduced LDL-C by 15 % compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg.

Homozygous Sitosterolaemia (Phytosterolaemia)

In a double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolaemia were randomised to receive Ezetimibe 10 mg (n=30) or placebo (n=7). Some patients were receiving other treatments (e.g., statins, resins). Ezetimibe significantly lowered the two major plant sterols, sitosterol and campesterol, by 21 % and 24 % from baseline, respectively. The effects of decreasing sitosterol on morbidity and mortality in this population are not known.

Aortic Stenosis

The Simvastatin and Ezetimibe for the Treatment of Aortic Stenosis (SEAS) study was a multi-center, double-blind, placebo-controlled study with a median duration of 4.4 years conducted in 1873 patients with asymptomatic aortic stenosis (AS), documented by Doppler-measured aortic peak flow velocity within the range of 2.5 to 4.0 m/s. Only patients who were considered not to require statin treatment for purposes of reducing atherosclerotic cardiovascular disease risk were enrolled. Patients were randomised 1:1 to receive placebo or co-administered ezetimibe 10 mg and simvastatin 40 mg daily.

The primary endpoint was the composite of major cardiovascular events (MCE) consisting of cardiovascular death, aortic valve replacement (AVR) surgery, congestive heart failure (CHF) as a result of progression of AS, nonfatal myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), hospitalisation for unstable angina, and nonhaemorrhagic stroke. The key secondary endpoints were composites of subsets of the primary endpoint event categories.

Compared to placebo, ezetimibe/simvastatin 10/40 mg did not significantly reduce the risk of MCE. The primary outcome occurred in 333 patients (35.3%) in the ezetimibe / simvastatin group and in 355 patients (38.2%) in the placebo group (hazard ratio in the ezetimibe / simvastatin group, 0.96; 95% confidence interval, 0.83 to 1.12; p = 0.59). Aortic valve replacement was performed in 267 patients (28.3%) in the ezetimibe / simvastatin group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; p = 0.97). Fewer patients had ischemic cardiovascular events in the ezetimibe / simvastatin group (n=148) than in the placebo group (n=187) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; p = 0.02), mainly because of the smaller number of patients who underwent coronary artery bypass grafting.

Cancer occurred more frequently in the ezetimibe / simvastatin group (105 versus 70, p = 0.01). The clinical relevance of this observation is uncertain as in the bigger SHARP trial the total number of patients with any incident cancer (438 in the ezetimibe/ simvastatin versus 439 placebo group) did not differ. In addition, in the IMPROVE-IT trial the total number of patients with any new malignancy (853 in the ezetimibe/simvastatin group versus 863 in the simvastatin group) did not differ significantly and therefore the finding of SEAS trial could not be confirmed by SHARP or IMPROVE-IT.

Pharmacokinetic properties

Absorption

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as Ezetimibe 10-mg tablets. Ezetimibe can be administered with or without food.

Distribution

Ezetimibe and ezetimibe-glucuronide are bound 99.7 % and 88 to 92 % to human plasma proteins, respectively.

Biotransformation

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93 % of the total radioactivity in plasma. Approximately 78 % and 11 % of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Special Populations

Paediatric population

The pharmacokinetics of ezetimibe are similar between children ≥6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

Older people

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with Ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic impairment

After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of

the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic impairment, Ezetimibe is not recommended in these patients.

Renal impairment

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 ml/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Gender

Plasma concentrations for total ezetimibe are slightly higher (approximately 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with Ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

Preclinical safety data

Atorvastatin

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.

Ezetimibe

Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (≥ 0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of Ezetimibe cannot be ruled out.

In co-administration studies with ezetimibe and statins the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2000 times the AUC level for the active metabolites).

In a series of *in vivo* and *in vitro* assays ezetimibe, given alone or co-administered with statins, exhibited no genotoxic potential. Long-term carcinogenicity tests on ezetimibe were negative.

Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1000 mg/kg/day. The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects.

EXPIRY DATE
Do not use later than the date of expiry.

PACKAGING INFORMATION
MODLIP EZ is available in 10 strips of 10 tablets each.

STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature not exceeding 30^{o}C, Protected from light and moisture.
Keep out of reach of children.

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