

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

TG TOR EZ

1. Generic Name

Atorvastatin Calcium & Ezetimibe Tablets

2. Qualitative and quantitative composition

Each film coated tablet contains:

Atorvastatin Calcium I.P Equivalent to Atorvastatin10 mg

Ezetimibe I.P. 10 mg

Excipients..... q.s.

Colours: Red Oxide of Iron USPNF & Titanium Dioxide I.P.

The excipients used are Lactose Monohydrate, Starch, Sodium Starch Glycolate, Povidone, Isopropyl Alcohol, Sodium Lauryl Sulphate, and Magnesium Stearate.

3. Dosage form and strength

Dosage Form: Film Coated Tablet

Strength: Atorvastatin – 10mg

Ezetimibe – 10mg

4. Clinical particulars

4.1 Therapeutic Indication

It is indicated for the treatment of patients with primary hypercholesterolemia

4.2 Posology and Method of Administration

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

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

Dose: As Prescribed by physician

4.3 Contraindications

Contraindicated in patients:

- With hypersensitivity to the active substance or to any of the excipients listed in
- With active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures
- treated with the hepatitis C antivirals glecaprevir/pibrentasvir
- 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.

4.4 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 haemorrhagic 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.

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.

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

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower

maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended.

Atorvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of Atorvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Paediatric population

No clinically significant effect on growth and sexual maturation was observed in a 3-year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight.

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/m², raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Ezetimibe

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 ($>3 \times \text{ULN}$) 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 $\geq 10,000$ 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.

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 to 10 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 hypercholesterolaemia 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.

Excipient

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Drugs Interactions

Atorvastatin

Effect of co-administered medicinal products on atorvastatin

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin. 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, some antivirals used in the treatment of HCV (e.g., elbasvir/grazoprevir), and

HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended.

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

CYP3A4 inducers

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport inhibitors

Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin. 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 (ratio of atorvastatin concentration: 0.74) when colestipol was co-administered with Atorvastatin. However, lipid effects were greater when Atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.

Colchicine

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

Effect of atorvastatin on co-administered medicinal products

Digoxin

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

Oral contraceptives

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

Warfarin

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

Paediatric population

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings in Special warnings and precautions for use should be taken into account for the paediatric population.

Drug interactions

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

	Atorvastatin
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Co-administered medicinal product and dosing regimen	Dose (mg)	Ratio of AUC ^{&}	Clinical Recommendation [#]
Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7 days	10 mg OD for 7 days	8.3	Co-administration with products containing glecaprevir or pibrentasvir is contraindicated.
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	In cases where co-administration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended.
Telaprevir 750 mg q8h, 10 days	20 mg, SD	7.9	
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	8.7	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	5.9	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	4.5	
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	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	3.4	
Itraconazole 200 mg OD, 4 days	40 mg SD	3.3	
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	2.5	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	2.3	
Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days	10 mg SD	1.95	The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing elbasvir or grazoprevir.
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	1.74	No specific recommendation.
Grapefruit Juice, 240 mL OD *	40 mg, SD	1.37	Concomitant intake of large quantities of grapefruit juice

			and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	1.51	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	1.33	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	1.18	No specific recommendation.
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 2 weeks	1.00	No specific recommendation.
Colestipol 10 g BID, 24 weeks	40 mg OD for 8 weeks	0.74**	No specific recommendation
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 17 days	10 mg OD for 15 days	0.66	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	0.59	No specific recommendation.
Rifampin 600 mg OD, 7 days (co-administered)	40 mg SD	1.12	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	0.20	
Gemfibrozil 600 mg BID, 7 days	40 mg SD	1.35	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40 mg SD	1.03	Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir 800 mg TID, 7 days	40 mg SD	2.3	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.

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

See Special warnings and precautions for use and Interaction with other medicinal products and other forms of interaction for clinical significance.

* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolised by CYP3A4. Intake of one 240 ml glass of

grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold.

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

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

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

Atorvastatin and dosing regimen	Co-administered medicinal product		
	Medicinal product/Dose (mg)	Ratio of AUC ^{&}	Clinical Recommendation
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	1.15	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	1.28 1.19	No specific recommendation.
80 mg OD for 15 days	* Phenazone, 600 mg SD	1.03	No specific recommendation.
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	1.08	No specific recommendation.
10 mg, OD for 4 days	Fosamprenavir 1400 mg BID, 14 days	0.73	No specific recommendation.
10 mg OD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	0.99	No specific recommendation.

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

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

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

Ezetimibe

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Antacids

Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Cholestyramine

Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55 %. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding Ezetimibe to cholestyramine may be lessened by this interaction.

Fibrates

In patients receiving fenofibrate and Ezetimibe, physicians should be aware of the possible risk of cholelithiasis and gallbladder disease.

If cholelithiasis is suspected in a patient receiving Ezetimibe and fenofibrate, gallbladder investigations are indicated and this therapy should be discontinued.

Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold respectively).

Co-administration of Ezetimibe with other fibrates has not been studied.

Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile but not in all species. A lactogenic risk associated with the therapeutic use of Ezetimibe cannot be ruled out.

Statins

No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

Ciclosporin

In a study of eight post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of ciclosporin, a single 10-mg dose of Ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal impairment who was receiving ciclosporin and multiple other medications demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100-mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating Ezetimibe in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe and ciclosporin.

Anticoagulants

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had Ezetimibe added to warfarin or fluindione. If Ezetimibe is added to

warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

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. Studies in animals have shown toxicity to reproduction.

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

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

Breast-feeding

It is unknown whether atorvastatin or its metabolites are excreted in human milk. 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 breast-feeding.

Fertility

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

Ezetimibe

Pregnancy

Ezetimibe co-administered with a statin is contraindicated during pregnancy and lactation.

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.

4.7 Effects On Ability to Drive and Use Machines

Atorvastatin

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

Ezetimibe

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.

4.8 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 ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); 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

Paediatric patients aged from 10 to 17 years of age treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. No clinically significant effect on growth and sexual maturation was observed in a 3-year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight. The safety and tolerability profile in paediatric patients was similar to the known safety profile of atorvastatin in adult patients.

The clinical safety database includes safety data for 520 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 121 patients were in the age range of 6 to 9, and 392 patients were in the age range of 10 to 17. Based on the data available, the frequency, type and severity of adverse reactions in children is similar to adults.

The following adverse events have been reported with some statins:

- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy.
- 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).

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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; gastro oesophageal 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; cholecystitis	cholelithiasis;	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 ($> 3 \times \text{ULN}$, 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 ($\geq 3 \times \text{ULN}$, 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 ($\geq 10 \times \text{ULN}$). 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 ($\geq 3 \times \text{ULN}$, 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 ($\geq 10 \times \text{ULN}$). 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 up titrated 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 $\geq 10,000$ IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases ($\geq 3 \times \text{ULN}$) 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).

4.9 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.

Ezetimibe

In Reported 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 over dosage 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Atorvastatin

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

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

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

Ezetimibe

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 hypercholesterolaemia patients, Ezetimibe inhibited intestinal cholesterol absorption by 54 %, compared with placebo.

5.2 Pharmacodynamics Properties

Atorvastatin

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

Atorvastatin has been shown to reduce concentrations of Total-C (30% - 46%), LDL-C (41% - 61%), Apo lipoprotein 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.

Homozygous familial hypercholesterolaemia

In a multicentre 8 week open-label compassionate-use study with an optional extension phase of variable length, 335 patients were enrolled, 89 of which were identified as homozygous

familial hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDL-C was approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid- Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomised, double- blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects of atorvastatin were statistically significant (p=0.02). The effect of intensive lipid lowering on cardiovascular endpoints (e. g. need for revascularisation, non-fatal myocardial infarction, and coronary death) was not investigated in this study.

In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L \pm 0.8 (78.9 mg/dl \pm 30) from baseline 3.89 mmol/L \pm 0.7 (150 mg/dl \pm 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/L \pm 0.7 (110 mg/dl \pm 26) from baseline 3.89 mmol/L \pm 0.7 (150 mg/dl \pm 26) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009), and mean apolipoprotein B by 39.1% (pravastatin: -22.0%, p<0.0001). Atorvastatin increased mean HDL-C by 2.9% (pravastatin: +5.6%, p=NS). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).

Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower dose strengths.

The safety and tolerability profiles of the two treatment groups were comparable.

The effect of intensive lipid lowering on major cardiovascular endpoints was not investigated in this study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown.

Acute coronary syndrome

In the MIRACL study, atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo n=1,548) with an acute coronary syndrome (non Q-wave MI or unstable angina). Treatment was initiated during the acute phase after hospital admission and lasted for a period of 16 weeks. Treatment with atorvastatin 80 mg/day increased the time to occurrence of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischaemia requiring hospitalization, indicating a risk reduction by 16% (p=0.048). This was mainly due to a 26% reduction in re-hospitalisation for angina pectoris with evidence of myocardial ischaemia (p=0.018). The other secondary endpoints did not reach statistical significance on their own (overall: Placebo: 22.2%, Atorvastatin: 22.4%).

The safety profile of atorvastatin in the MIRACL study was consistent with what is described in Undesirable effects.

Prevention of cardiovascular disease

The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomised, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5 mmol/L (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥ 55 years, smoking, diabetes, and history of CHD in a first-degree relative, TC: HDL-C > 6 , peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, and proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.

Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction¹ (%)	p-value
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events	20%	389 vs. 483	1.9%	0.0008
and revascularization procedures	29%	178 vs 247	1.4%	0.0006
Total coronary events				

¹Based on difference in crude events rates occurring over a median follow-up of 3.3 years.

CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p=0.17 and 74 vs. 82 events, p=0.51). In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non-fatal MI) was significantly reduced by atorvastatin in patients treated with amlodipine (HR 0.47 (0.32-0.69), p=0.00008), but not in those treated with atenolol (HR 0.83 (0.59-1.17), p=0.287).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomised, double-blind, multicentre, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 4.14 mmol/L (160 mg/dl) and TG ≤ 6.78 mmol/L (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or microalbuminuria.

Patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9 years.

The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction¹ (%)	p-value
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	Reduction (%)			
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs 64	1.9%	0.0070
Strokes (Fatal and non-fatal)	48%	21 vs. 39	1.3%	0.0163

¹Based on difference in crude events rates occurring over a median follow-up of 3.9 years.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p=0.0592).

Recurrent stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years) and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71-0.99; p=0.03 after adjustment for baseline factors) compared to placebo. All-cause mortality was 9.1% (216/2365) for atorvastatin versus 8.9% (211/2366) for placebo.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo.

- The risk of hemorrhagic stroke was increased in patients who entered the study with prior hemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57), and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).

- The risk of hemorrhagic stroke was increased in patients who entered the study with prior lacunar infarct (20/708 for atorvastatin versus 4/701 for placebo; HR 4.99; 95% CI, 1.71-14.61), but the risk of ischemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95% CI, 0.57-1.02). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive atorvastatin 80 mg/day.

All-cause mortality was 15.6% (7/45) for atorvastatin versus 10.4% (5/48) in the subgroup of patients with prior hemorrhagic stroke. All-cause mortality was 10.9% (77/708) for atorvastatin versus 9.1% (64/701) for placebo in the subgroup of patients with prior lacunar infarct.

Paediatric population

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 6-17 years' old

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of atorvastatin was conducted in children and adolescents with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL-C ≥ 4 mmol/L. A total of 39 children and adolescents, 6 to 17 years of age, were enrolled. Cohort A included 15 children, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 children, 10 to 17 years of age and at Tanner Stage ≥ 2 .

The initial dose of atorvastatin was 5 mg daily of a chewable tablet in Cohort A and 10 mg daily of a tablet formulation in Cohort B. The atorvastatin dose was permitted to be doubled if a subject had not attained target LDL-C of < 3.35 mmol/L at Week 4 and if atorvastatin was well tolerated.

Mean values for LDL-C, TC, VLDL-C, and Apo B decreased by Week 2 among all subjects. For subjects whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first assessment, after dose escalation. The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether subjects remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures.

In a second open label, single arm study, 271 males and female HeFH children 6-15 years of age were enrolled and treated with atorvastatin for up to three years. Inclusion in the study required confirmed HeFH and a baseline LDL-C level ≥ 4 mmol/L (approximately 152 mg/dL). The study included 139 children at Tanner 1 developmental stage (generally ranging from 6-10 years of age). The dosage of atorvastatin (once daily) was initiated at 5 mg (chewable tablet) in children less than 10 years of age. Children age 10 and above were initiated at 10 mg atorvastatin (once daily). All children could titrate to higher doses to achieve a target of < 3.35 mmol/L LDL-C. The mean weighted dose for children aged 6 to 9 years was 19.6 mg and the mean weighted dose for children aged 10 years and above was 23.9 mg.

The mean (+/- SD) baseline LDL-C value was 6.12 (1.26) mmol/L which was approximately 233 (48) mg/dL. See table 3 below for final results.

The data were consistent with no drug effect on any of the parameters of growth and development (i.e., height, weight, BMI, Tanner stage, Investigator assessment of Overall Maturation and Development) in paediatric and adolescent subjects with HeFH receiving atorvastatin treatment over the 3-year study. There was no Investigator-assessed drug effect noted in height, weight, BMI by age or by gender by visit.

TABLE. Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia (mmol/L)

Time point	N	TC (S.D.)	LDL-C (S.D.)	HDL-C (S.D.)	TG (S.D.)	Apo B (S.D.)#
Baseline	271	7.86(1.30)	6.12(1.26)	1.314(0.2663)	0.93(0.47)	1.42(0.28)**
Month 30	206	4.95(0.77)*	3.25(0.67)	1.327(0.2796)	0.79(0.38)*	0.90(0.17)*
Month 36/ET	240	5.12(0.86)	3.45(0.81)	1.308(0.2739)	0.78(0.41)	0.93(0.20)***

TC= total cholesterol; LDL-C = low density lipoprotein cholesterol-C; HDL-C = high density lipoprotein cholesterol-C; TG = triglycerides; Apo B = apolipoprotein B; "Month 36/ET" included final visit data for subjects who ended participation prior to the scheduled 36 month

time point as well as full 36 month data for subjects completing the 36 month participation; “*”= Month 30 N for this parameter was 207; “***”= Baseline N for this parameter was 270; “****” = Month 36/ET N for this parameter was 243; “#”=g/L for Apo B.

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 10-17 years’ old

In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (FH) or severe hypercholesterolaemia were randomised to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was >3.36 mmol/L. Atorvastatin significantly decreased plasma levels of Total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase. The mean achieved LDL-C value was 3.38 mmol/L (range: 1.81-6.26 mmol/L) in the atorvastatin group compared to 5.91 mmol/L (range: 3.93-9.96 mmol/L) in the placebo group during the 26-week double-blind phase.

An additional paediatric study of atorvastatin versus colestipol in patients with hypercholesterolaemia aged 10-18 years demonstrated that atorvastatin (N=25) caused a significant reduction in LDL-C at week 26 (p<0.05) compared with colestipol (N=31).

A compassionate use study in patients with severe hypercholesterolaemia (including homozygous hypercholesterolaemia) included 46 paediatric patients treated with atorvastatin titrated according to response (some subjects received 80 mg atorvastatin per day). The study lasted 3 years: LDL-cholesterol was lowered by 36%.

The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

The European Medicines Agency has waived the obligation to submit the results of studies with atorvastatin in children aged 0 to less than 6 years in the treatment of heterozygous hypercholesterolaemia and in children aged 0 to less than 18 years in the treatment of homozygous familial hypercholesterolaemia, combined (mixed) hypercholesterolaemia, primary hypercholesterolaemia and in the prevention of cardiovascular events.

5.3 Pharmacokinetic Properties

Atorvastatin

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 metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are

further metabolised via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination

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

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special populations

Elderly

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

Paediatric population

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.

Renal impairment

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

Hepatic impairment

Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in 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

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.

Elderly

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 \leq 30 ml/min/1.73 m²), 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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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

Ezetimibe

Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (\geq 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.

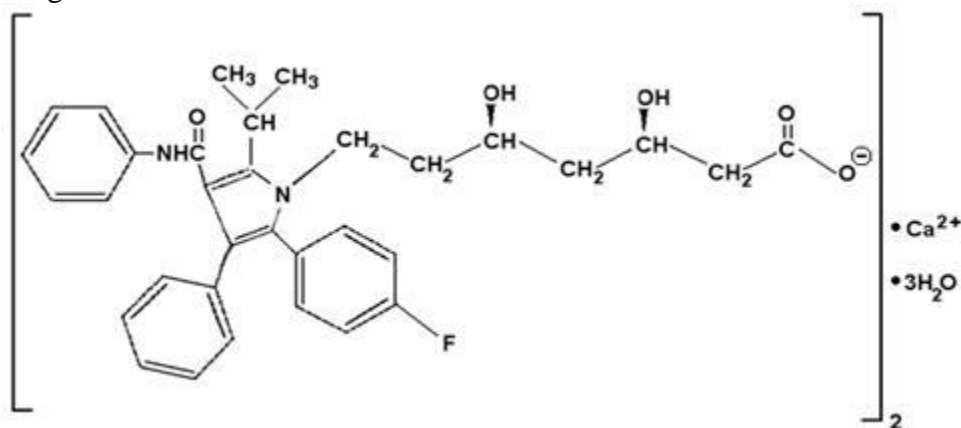
Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1000 mg/kg/day. The co-administration 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.

7. DESCRIPTION

Atorvastatin Calcium & Ezetimibe Tablets is indicated for the treatment of patients with primary hypercholesterolemia.

Atorvastatin Calcium

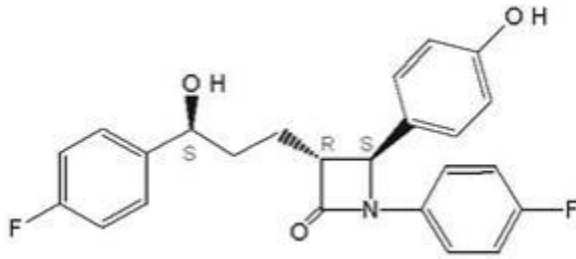
Atorvastatin Calcium is calcium salt of ($\beta R, 8R$)-2-(4-fluorophenyl)- α, δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder. It is freely soluble in methanol; slightly soluble in ethanol (95%) and very slightly soluble in water.

Ezetimibe

Ezetimibe is (3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-2-azetidinone. The empirical formula of Ezetimibe is $C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.4. Its structural formula is:



Ezetimibe is white to off white, crystalline powder. It is freely soluble in methanol, in ethanol and in acetone.

Atorvastatin Calcium & Ezetimibe Tablets are light pink, oval, biconvex, film coated tablets with break line on one side and plain on other side. The excipients used are Lactose Monohydrate, Starch, Sodium Starch Glycolate, Povidone, Isopropyl Alcohol, Sodium Lauryl Sulphate, and Magnesium Stearate.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not Available

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

TG TOR EZ is available in blister strip of 10 tablets.

8.4 Storage and Handling Instructions

STORE IN A COOL & DRY PLACE, PROTECTED FROM LIGHT.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the user

Atorvastatin Calcium & Ezetimibe Tablets

TG TOR EZ

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- if you have any further questions, ask your doctor, pharmacist or nurse.
- this medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- if you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

1. What TG TOR EZ is and what it is used for
2. What you need to know before you take TG TOR EZ
3. How to take TG TOR EZ
4. Possible side effects
5. How to store TG TOR EZ
6. Contents of the pack and other information

9.1. What TG TOR EZ is and what it is used for

TG TOR EZ is combination of Atorvastatin (belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines. Atorvastatin is used to lower lipids known as

cholesterol and triglycerides in the blood when a low fat diet and life style changes on their own have failed. If you are at an increased risk of heart disease, Atorvastatin can also be used to reduce such risk even if your cholesterol levels are normal. You should maintain a standard cholesterol lowering diet during treatment.) and EZETIMIBE (EZETIMIBE is a medicine to lower increased levels of cholesterol. EZETIMIBE lowers levels of total cholesterol, “bad” cholesterol (LDL cholesterol), and fatty substances called triglycerides in the blood. In addition, EZETIMIBE raises levels of “good” cholesterol (HDL cholesterol)

Ezetimibe, the active ingredient of EZETIMIBE, works by reducing the cholesterol absorbed in your digestive tract. EZETIMIBE adds to the cholesterol-lowering effect of statins, a group of medicines that reduce the cholesterol your body makes by itself. Cholesterol is one of several fatty substances found in the bloodstream. Your total cholesterol is made up mainly of LDL and HDL cholesterol. LDL cholesterol is often called “bad” cholesterol because it can build up in the walls of your arteries forming plaque. Eventually this plaque build-up can lead to a narrowing of the arteries. This narrowing can slow or block blood flow to vital organs such as the heart and brain. This blocking of blood flow can result in a heart attack or stroke. HDL cholesterol is often called “good” cholesterol because it helps keep the bad cholesterol from building up in the arteries and protects against heart disease. Triglycerides are another form of fat in your blood that may increase your risk for heart disease.

It is used for patients who cannot control their cholesterol levels by cholesterol lowering diet alone. You should stay on your cholesterol lowering diet while taking this medicine. TG TOR EZ is used for the treatment of patients with primary hypercholesterolemia.

9.2. What you need to know before you take TG TOR EZ

Do not take TG TOR EZ:

- If you are allergic to TG TOR EZ or any of the other ingredients of this medicine
- If you have or have ever had a disease which affects the liver
- If you have had any unexplained abnormal blood tests for liver function
- If you are a woman able to have children and not using reliable contraception
- If you are pregnant or trying to become pregnant
- If you are breast-feeding
- If you use the combination of glecaprevir/pibrentasvir in the treatment of hepatitis C

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking TG TOR EZ:

- if you have severe respiratory failure
- if you are taking or have taken in the last 7 days a medicine called fusidic acid, (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and TG TOR EZ can lead to serious muscle problems (rhabdomyolysis)
- If you have had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes
- If you have kidney problems
- If you have an under-active thyroid gland (hypothyroidism)
- If you have had repeated or unexplained muscle aches or pains, a personal history or family history of muscle problems
- If you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other ‘-statin’ or ‘-fibrate’ medicines)

- If you regularly drink a large amount of alcohol
- If you have a history of liver disease
- If you are older than 70 years

Talk to your doctor or pharmacist before taking EZETIMIBE.

- Tell your doctor about all your medical conditions including allergies.
- Your doctor should do a blood test before you start taking EZETIMIBE with a statin. This is to check how well your liver is working.
- Your doctor may also want you to have blood tests to check how well your liver is working after you start taking EZETIMIBE with a statin.

If you have moderate or severe liver problems, EZETIMIBE is not recommended.

The safety and efficacy of the combined use of EZETIMIBE and certain cholesterol lowering medicines, the fibrates have not been established

If any of these apply to you, your doctor will need to carry out a blood test before and possibly during your TG TOR EZ treatment to predict your risk of muscle related side effects. The risk of muscle related side effects e.g. rhabdomyolysis is known to increase when certain medicines are taken at the same time (see section 2 “Other medicines and TG TOR EZ”).

Also tell your doctor or pharmacist if you have a muscle weakness that is constant. Additional tests and medicines may be needed to diagnose and treat this.

While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.

Children and adolescents

Do not give this medicine to children and adolescents (6 to 17 years of age) unless prescribed by a specialist because there are limited data on safety and efficacy.

Do not give this medicine to children less than 6 years old because there is no information in this age group.

Other medicines and TG TOR EZ

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. There are some medicines that may change the effect of TG TOR EZ or their effect may be changed by TG TOR EZ. This type of interaction could make one or both of the medicines less effective. Alternatively, it could increase the risk or severity of side-effects, including the important muscle wasting condition known as rhabdomyolysis

- Medicines used to alter the way your immune system works, e.g. ciclosporin
- Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole, rifampin, fusidic acid
- Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, colestipol
- Some calcium channel blockers used for angina or high blood pressure, e.g. amlodipine, diltiazem; medicines to regulate your heart rhythm e.g. digoxin, verapamil, amiodarone
- Medicines used in the treatment of HIV e.g. ritonavir, lopinavir, atazanavir, indinavir, darunavir, the combination of tipranavir/ritonavir etc.
- Some medicines used in the treatment of hepatitis C e.g. telaprevir, boceprevir and the combination of elbasvir/grazoprevir
- Other medicines known to interact with TG TOR EZ include ezetimibe (which lowers cholesterol), warfarin (which reduces blood clotting), oral contraceptives, stiripentol (an anti-convulsant for epilepsy), cimetidine (used for heartburn and peptic ulcers), phenazone (a painkiller), colchicine (used to treat gout), and antacids (indigestion products containing aluminium or magnesium)

- Medicines obtained without a prescription: St John's Wort
- If you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using this medicine. Your doctor will tell you when it is safe to restart TG TOR EZ. Taking TG TOR EZ with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis). See more information regarding rhabdomyolysis in section 4.
- Ciclosporin (often used in organ transplant patients)
- Medicines with an active ingredient to prevent blood clots, such as warfarin, phenprocoumon, acenocoumarol or fluindione (anticoagulants)
- Cholestyramine (also used to lower cholesterol), because it affects the way EZETIMIBE works
- Fibrates (also used to lower cholesterol)

TG TOR EZ with food and drink

See section 3 for instructions on how to take TG TOR EZ. Please note the following:

Grapefruit juice

Do not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of TG TOR EZ.

Alcohol

Avoid drinking too much alcohol while taking this medicine. See section 2 "Warnings and precautions" for details.

- anti-coagulants to thin your blood (such as warfarin)
- Other medicines to control levels of fat in the blood (such as, statins or fibrates). This is because taking a statin or another fibrate in addition to **TG TOR EZ 160 mg** may increase the risk of muscle problems
- a particular class of medicines to treat diabetes (such as rosiglitazone or pioglitazone)
- cyclosporin (an immunosuppressant)

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking TG TOR EZ.

Pregnancy and breast-feeding

Do not take TG TOR EZ if you are pregnant, or if you are trying to become pregnant.

Do not take TG TOR EZ if you are able to become pregnant unless you use reliable contraceptive measures.

Do not take TG TOR EZ if you are breast-feeding.

The safety of TG TOR EZ during pregnancy and breast-feeding has not yet been proven. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Normally this medicine does not affect your ability to drive or operate machines. However, do not drive if this medicine affects your ability to drive. Do not use any tools or machines if your ability to use them is affected by this medicine.

9.3. How to take TG TOR EZ

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should maintain also during therapy with TG TOR EZ.

TG TOR EZ tablets should be swallowed whole with a drink of water, try to take your tablet at the same time every day. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- Before starting EZETIMIBE, you should be on a diet to lower your cholesterol.
- You should keep on this cholesterol lowering diet whilst taking EZETIMIBE

The duration of treatment with TG TOR EZ is determined by your doctor.

Please ask your doctor if you think that the effect of TG TOR EZ is too strong or too weak.

People with kidney problems

If you have kidney problems, your doctor may tell you to take a lower dose. Ask your doctor or pharmacist about this.

Use in children and adolescents

The use of TG TOR EZ is not recommended in children and young people under 18 years.

If you take more TG TOR EZ than you should

If you accidentally take too many TG TOR EZ tablets (more than your usual daily dose), contact your doctor or nearest hospital for advice.

If you forget to take TG TOR EZ

Talk to your doctor or pharmacist because your cholesterol may rise again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you stop taking TG TOR EZ

Do not stop taking TG TOR EZ unless your doctor tells you to, or the tablets make you feel unwell. This is because you require long-term treatment. If your doctor stops your medicine, do not keep any leftover tablets unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any of the following serious side effects, stop taking your tablets and tell your doctor immediately or go to the nearest hospital accident and emergency department.

Rare: may affect up to 1 in 1,000 people

- Serious allergic reaction which causes swelling of the face, tongue and throat that can cause great difficulty in breathing.
- Serious illness with severe peeling and swelling of the skin, blistering of the skin, mouth, eyes, genitals and fever. Skin rash with pink-red blotches especially on palms of hands or soles of feet which may blister.
- Muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown (rhabdomyolysis). The abnormal muscle breakdown does not always go away, even after you have stopped taking TG TOR EZ, and it can be life-threatening and lead to kidney problems.

Very rare: may affect up to 1 in 10,000 people

- If you experience problems with unexpected or unusual bleeding or bruising, this may be suggestive of a liver complaint. You should consult your doctor as soon as possible.

Stop taking TG TOR EZ and see a doctor straight away, if you notice any of the following serious side effects - you may need urgent medical treatment:

Uncommon: may affect up to 1 in 100 people

- cramps or painful, tender or weak muscles - these may be signs of muscle inflammation or breakdown, which can cause kidney damage or even death
- stomach pain - this may be a sign that your pancreas is inflamed (pancreatitis)
- chest pain and feeling breathless - these may be signs of a blood clot in the lung (pulmonary embolism)
- pain, redness or swelling in the legs - these may be signs of a blood clot in the leg (deep vein thrombosis)

Rare: may affect up to 1 in 1,000 people

- allergic reaction - the signs may include swelling of the face, lips, tongue or throat, which may cause difficulty in breathing
- yellowing of the skin and whites of the eyes (jaundice), or an increase in liver enzymes - these may be signs of an inflamed liver (hepatitis)

Not known: it is not known how often these happen

- severe skin rash which reddens, peels and swells and looks like a severe burn
- long-term lung problems

Stop taking TG TOR EZ and see a doctor straight away, if you notice any of the side effects above.

Other possible side effects with TG TOR EZ

Common: may affect up to 1 in 10 people

- inflammation of the nasal passages, pain in the throat, nose bleed
- allergic reactions
- increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels), increase in blood creatine kinase
- headache
- nausea, constipation, wind, indigestion, diarrhoea
- joint pain, muscle pain and back pain
- blood test results that show your liver function can become abnormal
- diarrhoea
- stomach pain
- wind (flatulence)
- feeling sick (nausea)
- being sick (vomiting)
- raised levels of liver enzymes in the blood - shown in tests
- increase in homocysteine (too much of this amino acid in the blood has been associated to a higher risk of coronary heart disease, stroke and peripheral vascular disease, although a causal link has not been established)
- abdominal pain; diarrhoea; flatulence; feeling tired
- Elevations in some laboratory blood tests of liver function (transaminases); headache; muscle pain, tenderness or weakness.

Uncommon: may affect up to 1 in 100 people

- anorexia (loss of appetite), weight gain, decreases in blood sugar levels (if you have diabetes you should continue careful monitoring of your blood sugar levels)
- having nightmares, insomnia
- dizziness, numbness or tingling in the fingers and toes, reductions of sensation to pain or touch, change in sense of taste, loss of memory
- blurred vision
- ringing in the ears and/or head
- vomiting, belching, abdominal pain upper and lower, pancreatitis (inflammation of the pancreas leading to stomach pain)
- hepatitis (liver inflammation)
- rash, skin rash and itching, hives, hair loss
- neck pain, muscle fatigue
- fatigue, feeling unwell, weakness, chest pain, swelling especially in the ankles (oedema), raised temperature
- urine tests that are positive for white blood cells
- headache
- gallstones
- reduced sex drive
- increase in creatinine (produced by the kidneys) - shown in tests
- elevations in some laboratory blood tests of liver (transaminases) or muscle (CK) function; cough; indigestion; heartburn; nausea; joint pain; muscle spasms; neck pain; decreased appetite, pain, chest pain, hot flush; high blood pressure.
- Additionally, when used with a statin, the following side effects were reported
- tingling sensation; dry mouth; itching; rash; hives; back pain; muscle weakness; pain in arms and legs; unusual tiredness or weakness; swelling, especially in the hands and feet.
- When used with fenofibrate, the following common side effect was reported:
- Abdominal pain.

Rare: may affect up to 1 in 1,000 people

- visual disturbance
- unexpected bleeding or bruising
- cholestasis (yellowing of the skin and whites of the eyes)

- tendon injury
- hair loss
- increase in urea (produced by the kidneys) - shown in tests
- skin is more sensitive to sunlight, sun lamps and sunbeds
- drop in haemoglobin (that carries oxygen in blood) and white blood cells - shown in tests

Very rare: may affect up to 1 in 10,000 people

- an allergic reaction - symptoms may include sudden wheezing and chest pain or tightness, swelling of the eyelids, face, lips, mouth, tongue or throat, difficulty breathing, collapse
- hearing loss
- Gynecomastia (breast enlargement in men).

Not known: frequency cannot be estimated from the available data: Muscle weakness that is constant.

Possible side effects reported with some statins (medicines of the same type):

- Sexual difficulties
- Depression
- Breathing problems including persistent cough and/or shortness of breath or fever
- Diabetes.
- muscle breakdown
- complications of gallbladder stones
- Feeling exhausted (fatigue).

Additionally, the following side effects have been reported in general use: dizziness; muscle aches; liver problems; allergic reactions including rash and hives; raised red rash, sometimes with target-shaped lesions (erythema multiforme); muscle pain, tenderness or weakness; muscle breakdown; gallstones or inflammation of the gallbladder (which may cause abdominal pain, nausea, vomiting); inflammation of the pancreas often with severe abdominal pain; constipation, reduction in blood cell counts, which may cause bruising/bleeding (thrombocytopenia); tingling sensation; depression: unusual tiredness or weakness; shortness of breath.

This is more likely if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure. Your doctor will monitor you while you are taking this medicine.

9.5. How to store EZETIMIBE

STORE IN A COOL & DRY PLACE, PROTECTED FROM LIGHT..

9.6. Contents of the pack and other information

What EZETIMIBE contains

– The active substance is ezetimibe and Atorvastatin. The excipients used are Lactose Monohydrate, Starch, Sodium Starch Glycolate, Povidone, Isopropyl Alcohol, Sodium Lauryl Sulphate, and Magnesium Stearate.

What EZETIMIBE looks like and contents of the pack

TG TOR EZ is available in Blister strips of 10 tablets

10. DETAILS OF MANUFACTURER

Manufactured by:

Torrent Pharmaceuticals Ltd

32 No. Middle Camp, NH-10, East District, Gangtok, Sikkim – 737 135.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Lic No. M/563/2010 issued on 20.11.2017

12. DATE OF REVISION

Not Applicable

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

IN/ TG TOR EZ 10mg, 10mg/JUN-19/01/PI