ATOZET®

Ezetimibe / Atorvastatin

1. INDICATIONS AND USAGE

Hypercholesterolaemia

ATOZET is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate

- patients not appropriately controlled with a statin alone
- patients already treated with a statin and ezetimibe

ATOZET contains ezetimibe and atorvastatin. Atorvastatin has been shown to reduce the frequency of cardiovascular events *[see 10. CLINICAL STUDIES]*. A beneficial effect of ATOZET or ezetimibe on cardiovascular morbidity and mortality has not yet been demonstrated.

Homozygous Familial Hypercholesterolemia (HoFH)

ATOZET is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

2. DOSAGE AND ADMINISTRATION

2.1 General

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with ATOZET. The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response. ATOZET can be administered as a single dose at any time of the day, with or without food.

2.2 Adults

Primary Hypercholesterolemia

The dosage range of ATOZET is 10/10 to 10/80 mg once daily. The recommended starting dose of ATOZET is 10/10 or 10/20 mg once daily. Patients who require a larger reduction in LDL-C (more than

55%) may be started at 10/40 mg once daily. After initiation and/or upon titration of ATOZET, lipid levels should be analyzed within 2 or more weeks and dosage adjusted accordingly.

Dosage in Patients with Homozygous Familial Hypercholesterolemia

The dosage of ATOZET in patients with homozygous familial hypercholesterolemia is 10/40 or 10/80 mg daily. ATOZET should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.3 Pediatric Patients

Treatment with ATOZET is not recommended.

2.4 Geriatric Patients

No dosage adjustment is required for elderly patients.

2.5 Renal Impairment

No dosage adjustment is required for renally impaired patients.

2.6 Hepatic Impairment

No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Treatment with ATOZET is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score >9) liver dysfunction *[see 3. CONTRAINDICATIONS, 4. WARNINGS AND PRECAUTIONS, 4.5 Hepatic Impairment]*.

2.7 Coadministration with Bile Acid Sequestrants

Dosing of ATOZET should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

2.8 Cyclosporine, Clarithromycin, Itraconazole, or Certain HIV/HCV Antiviral Agents

In patients taking cyclosporine or the HIV protease inhibitors tipranavir plus ritonavir or the hepatitis C protease inhibitor telaprevir, therapy with ATOZET should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing ATOZET and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or the hepatitis C antiviral agents boceprevir, elbasvir, grazoprevir or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with ATOZET should be limited to 10/20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir, therapy with ATOZET should be limited to 10/40 mg, and appropriate clinical assessment is recommended to ensure that the

lowest dose necessary of ATOZET is employed *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*.

2.9 Other Concomitant Lipid-Lowering Therapy

The combination of ATOZET and fibrates is not recommended *[see 4. WARNINGS AND PRECAUTIONS, 4.6 Fibrates, and 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Other Interactions]*.

3. CONTRAINDICATIONS

- ATOZET is contraindicated in patients with hypersensitivity to ezetimibe, atorvastatin, or any of its inactive ingredients.
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding three times the upper limit of normal (ULN).
- Pregnancy and nursing *[see 6. USE IN SPECIFIC POPULATIONS, 6.1. Pregnancy and 6.2. Nursing Mothers]*.
- Atorvastatin is contraindicated in patients who are concomitantly treated with glecaprevir/pibrentasvir.

4. WARNINGS AND PRECAUTIONS

4.1 Myopathy/Rhabdomyolysis

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CPK values >10 times ULN. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ATOZET. ATOZET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected *[see 8. ADVERSE REACTIONS]*.

The risk of myopathy during treatment with statins is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C antiviral agents telaprevir, elbasvir, grazoprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with ATOZET and fibric acid derivatives, erythromycin, clarithromycin, elbasvir, grazoprevir, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of ATOZET should be considered when taken concomitantly with the aforementioned drugs *[see 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.2 CYP3A4 Interactions]*. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 1 *[see 2. DOSAGE AND ADMINISTRATION, 2.8 Cyclosporine, Clarithromycin, Itraconazole, or Certain HIV/HCV Antiviral Agents, and 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.2 CYP3A4 Interactions]*.

Table 1

Atorvastatin Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations for ATOZET
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir), gemfibrozil	Avoid ATOZET.
Other fibrates (except fenofibrate), fusidic acid	Not recommended with ATOZET.
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary.
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir), hepatitis C antiviral agents (boceprevir, elbasvir, grazoprevir)	Do not exceed 10/20 mg ATOZET daily.
HIV protease inhibitor (nelfinavir)	Do not exceed 10/40 mg ATOZET daily.

* Use with caution and with the lowest dose necessary

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin coadministered with colchicine, and caution should be exercised when prescribing ATOZET with colchicine *[see 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Other Interactions]*.

Reports of myopathy and/or rhabdomyolysis have been observed with HMG-CoA reductase inhibitors coadministered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to suspending ATOZET temporarily in patients taking daptomycin *[see 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Other Interactions]*.

ATOZET therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal

failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

4.2 Aggravation of Myasthenia Gravis/Ocular Myasthenia

Statins may in rare instances aggravate the conditions in patients with myasthenia gravis or ocular myasthenia *[see 8. ADVERSE REACTIONS]*. ATOZET should be used with caution in patients with these conditions.

4.3 Liver Enzymes

In controlled coadministration trials in patients receiving ezetimibe with atorvastatin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed *[see 8. ADVERSE REACTIONS]*.

Atorvastatin, like some other lipid-lowering therapies, has been associated with biochemical abnormalities of liver function.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with ATOZET and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with ATOZET, promptly interrupt therapy. If an alternate etiology is not found, do not restart ATOZET.

ATOZET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin *[see 3. CONTRAINDICATIONS]*.

4.4 Endocrine Function

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if ATOZET is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Increases in hemoglobin A1c (HbA1c) and fasting serum glucose levels have been reported with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, including atorvastatin. For some

patients, at high risk of diabetes mellitus, hyperglycemia was sufficient to shift them to the diabetes status. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins. Periodic monitoring of these patients is recommended.

4.5 Hepatic Impairment

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

4.6 Fibrates *[see 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Other Interactions]*

Gemfibrozil: Concomitant administration of ATOZET with gemfibrozil should be avoided.

Fenofibrate: Caution should be used when prescribing ATOZET and fenofibrate, as fenofibrate can cause myopathy when given alone.

If cholelithiasis is suspected in a patient receiving ATOZET and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered [see the product labeling for fenofibrate and fenofibric acid].

Other fibrates: The coadministration of ezetimibe with other fibrates has not been studied. Therefore, coadministration of ATOZET and other fibrates is not recommended.

4.7 Fusidic acid

Patients on fusidic acid treated concomitantly with ATOZET may have an increased risk of myopathy/rhabdomyolysis *[see 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Other Interactions]*. Coadministration with fusidic acid is not recommended. In patients where the use of systemic fusidic acid is considered essential, ATOZET should be discontinued throughout the duration of fusidic acid treatment. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for coadministration of ATOZET and fusidic acid should only be considered on a case-by-case basis under close medical supervision.

4.8 Anticoagulants

If ATOZET is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored *[see 5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS, 5.3 Other Interactions]*.

4.9 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin 80 mg group compared to placebo. The incidence of fatal hemorrhagic stroke was similar across treatment groups. The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group as compared to the placebo group. Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group. The potential risk of hemorrhagic stroke should be carefully considered before initiating treatment with atorvastatin in patients with recent (1 to 6 months) stroke or TIA.

5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

5.1 ATOZET

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with atorvastatin.

Multiple mechanisms may contribute to potential interactions with HMG-CoA reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g., CYP3A4) and/or transporter (e.g., OATP1B) pathways may increase atorvastatin plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with atorvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

5.2 CYP3A4 Interactions

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolizing enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase. Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4.

Inhibitors of cytochrome P3A4 increase the risk of myopathy by reducing the elimination of the atorvastatin component of ATOZET *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of 80 mg atorvastatin with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone. Therefore, in patients taking clarithromycin, caution should be used when the ATOZET dose exceeds 10/20 mg *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis, and 2. DOSAGE AND ADMINISTRATION, 2.8 Cyclosporine, Clarithromycin, Itraconazole, or Certain HIV/HCV Antiviral Agents]*.

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of ATOZET should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing ATOZET, and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, or the hepatitis C protease inhibitor boceprevir, the dose of ATOZET should not exceed 10/20 mg and should be used with caution *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis, and 2. DOSAGE AND ADMINISTRATION, 2.8 Cyclosporine, Clarithromycin, Itraconazole, or Certain HIV/HCV Antiviral Agents]*. In patients taking the HIV protease inhibitor nelfinavir, the dose of ATOZET should not exceed 10/40 mg and close clinical monitoring is recommended.

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg. Therefore, in patients taking itraconazole, caution should be used when the ATOZET dose exceeds 10/20 mg.

Grapefruit Juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

Cyclosporine: In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of cyclosporine, 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 from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications,

including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls. 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 cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*.

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin alone. The coadministration of ATOZET with cyclosporine should be avoided *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*.

Table 2. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered Drug and Dosing Regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC[&]	Ratio of C_{max}[&]
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD[a] for 28 days	8.7	10.7
[#]Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days	10 mg SD[c]	9.4	8.6
[#]Glecaprevir 400 mg QD[a]/Pibrentasvir 120 mg QD[a], 7 days	10 mg QD[a] for 7 days	8.3	22.0
[#]Telaprevir 750 mg q8h[f], 10 days	20 mg SD[c]	7.9	10.6
[#]Elbasvir 50 mg QD[a]/grazoprevir 200 mg QD[a], 13 days	10 mg SD[c]	1.94	4.3
[#]Boceprevir 800 mg TID[d], 7 days	40 mg SD[c]	2.3	2.7
[#]Simeprevir 150 mg QD[a], 10 days	40 mg SD[c]	2.12	1.7
[#]Lopinavir 400 mg BID[b]/ritonavir 100 mg BID[b], 14 days	20 mg QD[a] for 4 days	5.9	4.7
[#,‡]Saquinavir 400 mg BID[b]/ritonavir 400 mg BID[b], 15 days	40 mg QD[a] for 4 days	3.9	4.3

#Clarithromycin 500 mg BID[b], 9 days	80 mg QD[a] for 8 days	4.5	5.4
#Darunavir 300 mg BID[b]/ritonavir 100 mg BID[b], 9 days	10 mg QD[a] for 4 days	3.4	2.2
#Itraconazole 200 mg QD[a], 4 days	40 mg SD[c]	3.3	1.20
#Letermovir 480 mg QD[a], 10 days	20 mg SD[c]	3.29	2.17
#Fosamprenavir 700 mg BID[b]/ritonavir 100 mg BID[b], 14 days	10 mg QD[a] for 4 days	2.5	2.8
#Fosamprenavir 1400 mg BID[b], 14 days	10 mg QD[a] for 4 days	2.3	4.0
#Nelfinavir 1250 mg BID[b], 14 days	10 mg QD[a] for 28 days	1.74	2.2
#Grapefruit juice, 240 mL QD[a,*]	40 mg SD[c]	1.37	1.16
Diltiazem 240 mg QD[a], 28 days	40 mg SD[c]	1.51	1.00
Erythromycin 500 mg QID[e], 7 days	10 mg SD[c]	1.33	1.38
Amlodipine 10 mg, single dose	80 mg SD[c]	1.18	0.91
Cimetidine 300 mg QID[e], 2 weeks	10 mg QD[a] for 2 weeks	1.00	0.89
Colestipol 10 g BID[b], 24 weeks	40 mg QD[a] for 8 weeks	NA	0.74**
Maalox TC® 30 mL QID[e], 17 days	10 mg QD[a] for 15 days	0.66	0.67
Efavirenz 600 mg QD[a], 14 days	10 mg for 3 days	0.59	1.01
#Rifampin 600 mg QD[a], 7 days (co-administered)[†]	40 mg SD[c]	1.12	2.9
#Rifampin 600 mg QD[a], 5 days (doses separated)[†]	40 mg SD[c]	0.20	0.60
#Gemfibrozil 600 mg BID[b], 7 days	40 mg SD[c]	1.35	1.00
#Fenofibrate 160 mg QD[a], 7 days	40 mg SD[c]	1.03	1.02

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

[#] See section **4. – WARNINGS AND PRECAUTIONS** and section **5. – DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS** for clinical significance.

* Greater increases in AUC (ratio of AUC up to 2.5) and/or C_{max} (ratio of C_{max} up to 1.71) have been reported with excessive grapefruit consumption (≥750 mL - 1.2 L/day).

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

† Due to the dual interaction mechanism of rifampin, 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 dose of saquinavir/ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore caution should be exercised and the lowest dose necessary should be used.

[a] Once daily

[b] Twice daily

[c] Single dose

[d] Three times daily

[e] Four times daily

[f] Every 8 hours

5.3 Other Interactions

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.

Coadministration of atorvastatin with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites approximately 35%; however, LDL-C reduction was not altered.

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction.

Fibrates *[see 4. WARNINGS AND PRECAUTIONS, 4.6 Fibrates]*:

Gemfibrozil: Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of ATOZET with gemfibrozil should be avoided.

In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available.

Fenofibrate: Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of fenofibrate, ATOZET should be administered with caution when used concomitantly with fenofibrate.

In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. This increase is not considered clinically significant.

Other fibrates: The safety and effectiveness of ezetimibe administered with other fibrates have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile *[see 12. ANIMAL PHARMACOLOGY]*. Although the relevance of this preclinical finding to humans is unknown, coadministration of ATOZET with other fibrates is not recommended until use in patients is studied.

Fusidic Acid: The risk of myopathy/rhabdomyolysis may be increased by concomitant administration of fusidic acid *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*.

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. There have been post-marketing reports of increased INR in patients who had ezetimibe added to warfarin or fluindione. Most of these patients were also on other medications *[see 4. WARNINGS AND PRECAUTIONS, 4.8 Anticoagulants]*.

Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

The effect of ATOZET on the prothrombin time has not been studied.

Inhibitors of Breast Cancer Resistant Protein (BCRP): Atorvastatin is a substrate of the efflux transporter BCRP. Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy; therefore, a dose adjustment of atorvastatin may be necessary. Coadministration of elbasvir and grazoprevir with atorvastatin increases plasma concentrations of atorvastatin by 1.9-fold due in part to CYP3A and/or BCRP inhibition; therefore, the dose of ATOZET should not exceed 10/20 mg daily in

patients receiving concomitant medication with products containing elbasvir or grazoprevir *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*.

Elbasvir and Grazoprevir: Elbasvir and grazoprevir are inhibitors of OATP1B1, OATP1B3, multi-drug resistance protein 1 (MDR1) and BCRP, thus they increase exposure to atorvastatin. Use with caution and lowest dose necessary. Dose of atorvastatin should not exceed 20 mg/day with concomitant use with elbasvir/grazoprevir.

Inducers of Cytochrome P450 3A4: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous coadministration 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.

Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Amlodipine: In a drug-drug interaction study in healthy subjects, coadministration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin that was not clinically meaningful.

Niacin: The risk of skeletal muscle effects may be enhanced when ATOZET is used in combination with niacin; a reduction in ATOZET dosage should be considered in this setting *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*.

Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin coadministered with colchicine, and caution should be exercised when prescribing ATOZET with colchicine.

Daptomycin: The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors and daptomycin *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*.

Glecaprevir and Pibrentasvir: Glecaprevir and pibrentasvir are inhibitors of OATP1B1, OATP1B3, MDR1 and BCRP, thus they increase exposure to atorvastatin and concomitant use with atorvastatin is contraindicated.

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia.

ATOZET

ATOZET is contraindicated during pregnancy. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, ATOZET may cause fetal harm when administered to pregnant women. ATOZET should be discontinued as soon as pregnancy is recognized *[see 3. CONTRAINDICATIONS]*. Advise females of reproductive potential to use effective contraception during treatment with ATOZET.

Ezetimibe

No clinical data on exposed pregnancies are available. Animal studies of ezetimibe administered alone do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

When ezetimibe was given with statins, no teratogenic effects were observed in embryo-fetal development studies in pregnant rats. In pregnant rabbits, a low incidence of skeletal malformations was observed.

Atorvastatin

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate to exclude a greater than or equal to three-to-four-fold increase in congenital anomalies over background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

6.2 Nursing Mothers

ATOZET

ATOZET is contraindicated in nursing mothers. Because of the potential for serious adverse reactions in a breastfed infant, women who are nursing should not take ATOZET.

Ezetimibe

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether ezetimibe is excreted into human breast milk.

Atorvastatin

There is no available information on the effects of atorvastatin on the breastfed infant or the effects of atorvastatin on milk production. It is not known whether atorvastatin is present in human milk, but it has been shown that another drug in this class passes into human milk and atorvastatin is present in rat milk.

6.3 Pediatric Use

There are insufficient data for the safe and effective use of ATOZET in pediatric patients.

7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies of the effects on the ability to drive and use machines have been performed. However, certain side effects that have been reported with ATOZET may affect some patients' ability to drive or operate machinery. Individual responses to ATOZET may vary *[see 8. ADVERSE REACTIONS]*.

8. ADVERSE REACTIONS

8.1 Clinical Trials Experience

Adults

ATOZET

ATOZET (or coadministration of ezetimibe and atorvastatin equivalent to ATOZET) has been evaluated for safety in more than 2400 patients in 7 clinical trials. ATOZET was generally well tolerated.

The following common (≥ 1/100, <1/10) or uncommon (≥ 1/1000, <1/100) drug-related adverse experiences were reported in patients taking ATOZET:

Infections and Infestations:

Uncommon: influenza

Psychiatric disorders:

Uncommon: depression; insomnia; sleep disorder

Nervous system disorders:

Uncommon: dizziness; dysgeusia; headache; paresthesia

Cardiac disorders:

Uncommon: sinus bradycardia

Vascular disorders:

Uncommon: hot flush

Respiratory, thoracic and mediastinal disorders:

Uncommon: dyspnea

Gastrointestinal disorders:

Common: diarrhea

Uncommon: abdominal discomfort; abdominal distension; abdominal pain; abdominal pain lower; abdominal pain upper; constipation; dyspepsia; flatulence; frequent bowel movements; gastritis; nausea; stomach discomfort

Skin and subcutaneous tissue disorders:

Uncommon: acne; urticaria

Musculoskeletal and connective tissue disorders:
Common: myalgia
Uncommon: arthralgia; back pain; muscle fatigue; muscle spasms; muscular weakness; pain in extremity

General disorders and administration site conditions:
Uncommon: asthenia; fatigue; malaise; edema

Investigations:
Uncommon: ALT and/or AST increased; alkaline phosphatase increased; blood CK increased; gamma-glutamyltransferase increased; hepatic enzyme increased; liver function test abnormal; weight increased

In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 0.6% for patients treated with ATOZET. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy *[see 4. WARNINGS AND PRECAUTIONS, 4.3 Liver Enzymes]*.

None of the patients treated with ATOZET had CK levels ≥10 X ULN.

8.2 Post-marketing Experience and Other Clinical Trial Experience

The following additional adverse reactions have been reported in post-marketing use with ATOZET or in clinical studies or post-marketing use with ezetimibe or atorvastatin:

Infections and infestations: nasopharyngitis

Blood and lymphatic system disorders: thrombocytopenia

Immune system disorders: hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria

Metabolism and nutrition disorders: decreased appetite; anorexia; hyperglycemia; hypoglycemia

Psychiatric disorders: nightmares

Nervous system disorders: hypesthesia; peripheral neuropathy; myasthenia gravis aggravated *[see 4. WARNINGS AND PRECAUTIONS, 4.2 Aggravation of Myasthenia Gravis/Ocular Myasthenia]*.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Eye disorders: vision blurred; visual disturbance; ocular myasthenia aggravated *[see 4. WARNINGS AND PRECAUTIONS, 4.2 Aggravation of Myasthenia Gravis/Ocular Myasthenia]*.

Ear and labyrinth disorders: tinnitus; hearing loss

Vascular disorders: hypertension

Respiratory, thoracic, and mediastinal disorders: cough; pharyngolaryngeal pain; epistaxis

Gastrointestinal disorders: dry mouth; pancreatitis; gastroesophageal reflux disease; eructation; vomiting

Hepatobiliary disorders: hepatitis; cholelithiasis; cholecystitis; cholestasis; fatal and non-fatal hepatic failure

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

Musculoskeletal and connective tissue disorders: myopathy/rhabdomyolysis *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*; neck pain; joint swelling; myositis; tendinopathy, sometimes complicated by rupture

There have been very rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents *[see 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis]*.

Reproductive system and breast disorders: gynecomastia

General disorders and administration site conditions: chest pain; pain; edema peripheral; pyrexia

Investigations: white blood cells urine positive

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

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/m^2, raised triglycerides, history of hypertension)

9. OVERDOSAGE

ATOZET

No specific treatment of overdosage with ATOZET can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hyperlipidemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolemia for 26 weeks, was generally well tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Atorvastatin

Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

10. CLINICAL STUDIES

In controlled clinical studies, ATOZET significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density

lipoprotein cholesterol (non-HDL-C), and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolemia.

Primary Hypercholesterolemia

ATOZET

In a multicenter, double-blind, placebo-controlled, clinical study in patients with hyperlipidemia, 628 patients were treated for up to 12 weeks and 246 for up to an additional 48 weeks. Patients were randomized to receive placebo, ezetimibe (10 mg), atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or coadministered ezetimibe and atorvastatin equivalent to ATOZET (10/10, 10/20, 10/40, and 10/80) in the 12-week study. After completing the 12-week study, eligible patients were assigned to coadministered ezetimibe and atorvastatin equivalent to ATOZET (10/10-10/80) or atorvastatin (10-80 mg/day) for an additional 48 weeks.

Patients receiving all doses of ATOZET were compared to those receiving all doses of atorvastatin. ATOZET lowered total-C, LDL-C, Apo B, TG, and non-HDL-C, and increased HDL-C significantly more than atorvastatin alone (see Table 3).

Table 3

Response to ATOZET in Patients with Primary Hyperlipidemia

(Mean[a] % Change from Untreated Baseline[b] at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C	Non-HDL-C
Pooled data (All ATOZET doses)[c]	255	-41	-56	-45	-33	+7	-52
Pooled data (All atorvastatin doses)[c]	248	-32	-44	-36	-24	+4	-41
Ezetimibe 10 mg	65	-14	-20	-15	-5	+4	-18
Placebo	60	+4	+4	+3	-6	+4	+4
ATOZET by dose							
10/10	65	-38	-53	-43	-31	+9	-49
10/20	62	-39	-54	-44	-30	+9	-50
10/40	65	-42	-56	-45	-34	+5	-52
10/80	63	-46	-61	-50	-40	+7	-58
Atorvastatin by dose							
10 mg	60	-26	-37	-28	-21	+6	-34
20 mg	60	-30	-42	-34	-23	+4	-39
40 mg	66	-32	-45	-37	-24	+4	-41
80 mg	62	-40	-54	-46	-31	+3	-51

[a] For triglycerides, median % change from baseline

[b] Baseline - on no lipid-lowering drug

[c] ATOZET pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, non-HDL-C, and significantly increased HDL-C compared to all doses of atorvastatin pooled (10-80 mg).

The changes in lipid endpoints after an additional 48 weeks of treatment with ATOZET (all doses) or with atorvastatin (all doses) were generally consistent with the 12-week data displayed above.

A multicenter, double-blind, controlled, 14-week study was conducted in 621 patients with heterozygous familial hypercholesterolemia (HeFH), coronary heart disease (CHD), or multiple cardiovascular risk factors (≥2), adhering to an NCEP Step I or stricter diet. All patients received atorvastatin 10 mg for a minimum of 4 weeks prior to randomization. Patients were then randomized to receive either coadministered ezetimibe and atorvastatin (equivalent to ATOZET 10/10) or atorvastatin 20 mg/day

monotherapy. Patients who did not achieve their LDL-C target goal after 4 and/or 9 weeks of randomized treatment were titrated to double the atorvastatin dose.

ATOZET 10/10 was significantly more effective than doubling the dose of atorvastatin to 20 mg in further reducing total-C, LDL-C, TG, and non-HDL-C. Results for HDL-C between the two treatment groups were not significantly different (see Table 4). In addition, at Week 4 significantly more patients receiving ATOZET 10/10 attained LDL-C <2.6 mmol/L (<100 mg/dL) compared to those receiving atorvastatin 20 mg, 12% vs. 2%. The baseline mean LDL-C levels for patients receiving ATOZET 10/10 and atorvastatin 20 mg were 186 mg/dL and 187 mg/dL, respectively.

Table 4

Response to ATOZET after 4 Weeks in Patients with CHD or Multiple Cardiovascular Risk Factors and an LDL-C ≥130 mg/dL

(Mean* % Change from Baseline†)

Treatment (Daily Dose)	N	Total-C	LDL-C	HDL-C	TG*	Non-HDL-C
ATOZET 10/10	305	-17‡	-24‡	+2	-9‡	-22‡
Atorvastatin 20 mg	316	-6	-9	+1	-4	-8

* For triglycerides, median % change from baseline

† Patients on atorvastatin 10 mg, then switched to ATOZET 10/10 or titrated to atorvastatin 20 mg

‡ p<0.05 for difference with atorvastatin

The Titration of Atorvastatin Versus Ezetimibe Add-On to Atorvastatin in Patients with Hypercholesterolemia (TEMPO) study, a multicenter, double-blind, controlled, 6-week study, included 184 patients with an LDL-C level ≥2.6 mmol/L and ≤4.1 mmol/L (≥100 mg/dL and ≤160 mg/dL) and at moderate high risk for coronary heart disease (CHD). All patients received atorvastatin 20 mg for a minimum of 4 weeks prior to randomization. Patients not at the optional NCEP ATP III LDL-C level (<2.6 mmol/L [<100 mg/dL]) were randomized to receive either coadministered ezetimibe and atorvastatin (equivalent to ATOZET 10/20) or atorvastatin 40 mg for 6 weeks.

ATOZET 10/20 was significantly more effective than doubling the dose of atorvastatin to 40 mg in further reducing total-C, LDL-C, Apo B and non-HDL-C. Results for HDL-C and TG between the two treatment groups were not significantly different (see Table 5). In addition, significantly more patients receiving ATOZET 10/20 attained LDL-C <2.6 mmol/L (<100 mg/dL) compared to those receiving atorvastatin 40 mg, 84% vs. 49%.

Table 5

Response to ATOZET in Patients with Primary Hypercholesterolemia

(Mean[a] % Change from Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
ATOZET 10/20	92	-20[c]	-31[c]	-21[c]	+3	-18	-27[c]
Atorvastatin 40 mg	92	-7	-11	-8	+1	-6	-10

[a] For triglycerides, median % change from baseline

[b] Patients on atorvastatin 20 mg, then switched to ATOZET 10/20 or titrated to atorvastatin 40 mg

[c] $p<0.05$ for difference with atorvastatin

The Ezetimibe Plus Atorvastatin Versus Atorvastatin Titration in Achieving Lower LDL-C Targets in Hypercholesterolemic Patients (EZ-PATH) study, a multicenter, double-blind, controlled, 6-week study, included 556 patients with an LDL-C level ≥1.8 mmol/L and ≤4.1 mmol/L (≥70 mg/dL and ≤160 mg/dL) and at high risk for coronary heart disease (CHD). All patients received atorvastatin 40 mg for a minimum of 4 weeks prior to randomization. Patients not at the optional NCEP ATP III LDL-C level <1.8 mmol/L (<70 mg/dL) were randomized to receive either coadministered ezetimibe and atorvastatin (equivalent to ATOZET 10/40) or atorvastatin 80 mg for 6 weeks.

ATOZET 10/40 was significantly more effective than doubling the dose of atorvastatin to 80 mg in further reducing total-C, LDL-C, Apo B, TG, and non-HDL-C. Results for HDL-C between the two treatment groups were not significantly different (see Table 6). In addition, significantly more patients receiving ATOZET 10/40 attained LDL-C <1.8 mmol/L (<70 mg/dL) compared to those receiving atorvastatin 80 mg, 74% vs. 32%.

Table 6

Response to ATOZET in Patients with Primary Hypercholesterolemia

(Mean[a] % Change from Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
ATOZET 10/40	277	-17[c]	-27[c]	-18[c]	0	-12[c]	-23[c]
Atorvastatin 80 mg	279	-7	-11	-8	-1	-6	-9

[a] For triglycerides, median % change from baseline

[b] Patients on atorvastatin 40 mg, then switched to ATOZET 10/40 or titrated to atorvastatin 80 mg

[c] $p<0.05$ for difference with atorvastatin

In a double-blind, placebo-controlled, 8-week study, 308 patients with hypercholesterolemia already receiving atorvastatin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (LDL-C goal based upon baseline LDL-C and CHD risk status) were randomized to receive either ezetimibe 10 mg or placebo in addition to their on-going atorvastatin therapy.

Among atorvastatin-treated patients not at LDL-C goal at baseline (~83%), significantly more patients randomized to ezetimibe coadministered with atorvastatin achieved their LDL-C goal at study endpoint compared to patients randomized to placebo coadministered with atorvastatin, 72% vs. 27%. Ezetimibe added to atorvastatin therapy lowered LDL-C significantly more than placebo added to atorvastatin therapy, 25% vs. 4%. In addition, ezetimibe added to atorvastatin therapy significantly decreased total-C, Apo B, and TG compared with placebo added to atorvastatin therapy.

In a multicenter, double-blind, controlled, 12-week, 2-phase study, 1539 high-cardiovascular-risk patients, with a LDL-C level between 100 and 160 mg/dL at baseline on atorvastatin 10 mg daily, were randomized to one of three treatment groups: atorvastatin 20 mg, rosuvastatin 10 mg, or coadministered ezetimibe and atorvastatin (equivalent to ATOZET 10/10). After 6 weeks of treatment (Phase I), based on a random allocation schedule established at the start of Phase I, patients taking atorvastatin 20 mg who failed to achieve a LDL-C level <100 mg/dL were switched to either atorvastatin 40 mg or coadministered ezetimibe and atorvastatin (equivalent to ATOZET 10/20) for 6 weeks (Phase II), and similar patients taking rosuvastatin 10 mg during Phase I were switched to either rosuvastatin 20 mg or coadministered ezetimibe and atorvastatin (equivalent to ATOZET 10/20) during Phase II. Reductions in LDL-C and comparisons between the ATOZET group and other treatment groups studied are shown in Table 7.

Table 7
Response to ATOZET* in High-Risk Patients with a LDL-C Level Between 100 and 160 mg/dL on Atorvastatin 10 mg Daily at Baseline

Treatment	N	Percent Change from Baseline†					
		Total-C	LDL-C	Apo B	TG‡	HDL-C	Non-HDL-C
Phase I							
Switched from atorvastatin 10 mg							
ATOZET 10/10	120	-13.5	-22.2	-11.3	-6.0	+0.6	-18.3
Atorvastatin 20 mg	480	-6.4§	-9.5§	-6.0¶	-3.9	-1.1	-8.1§
Rosuvastatin 10 mg	939	-7.7§	-13.0§	-6.9#	-1.1	+1.1	-10.6§
Phase II							

Switched from atorvastatin 20 mg							
ATOZET 10/20	124	-10.7	-17.4	-9.8	-5.9	+0.7	-15.1
Atorvastatin 40 mg	124	-3.8Þ	-6.9Þ	-5.4	-3.1	+1.7	-5.8Þ
Switched from rosuvastatin 10 mg							
ATOZET 10/20	231	-11.8	-17.1	-11.9	-10.2	+0.1	-16.2
Rosuvastatin 20 mg	205	-4.5Þ	-7.5Þ	-4.1Þ	-3.2ß	+0.8	-6.4Þ

* Coadministered ezetimibe and atorvastatin equivalent to ATOZET 10/10 or ATOZET 10/20

† M-Estimates (based on the method of Huber; 95% CI and p-value were obtained from fitting a robust Regression model with terms for treatment and baseline)

‡ Geometric mean percent changes from baseline in TG were calculated based on back-transformation via exponentiation of the model-based least square (LS) means and expressed as (geometric mean – 1) multiplied by 100

§ p<0.001 versus ATOZET 10/10

¶ p<0.01 versus ATOZET 10/10

# p<0.05 versus ATOZET 10/10

Þ p<0.001 versus ATOZET 10/20

ß p<0.05 versus ATOZET 10/20

Table 7 does not contain data comparing the effects of ATOZET 10/10 or 10/20 to doses higher than atorvastatin 40 mg or rosuvastatin 20 mg.

Ezetimibe

In two multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, ezetimibe significantly lowered total-C (-13%), LDL-C (-19%), Apo B (-14%), TG (-8%), and non-HDL-C (-17%) and increased HDL-C (+3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, and baseline LDL-C.

Atorvastatin

In a placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin 10 mg on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients, 40-80 years old, with TC levels ≤251 mg/dL (6.5 mmol/L) and at least three cardiovascular risk factors. Patients were followed for a median duration of 3.3 years. Atorvastatin 10 mg significantly (p=0.0005) reduced the rate of coronary events (either fatal coronary heart disease [46 events in the placebo group vs. 40 events in the atorvastatin group] or nonfatal MI [108 events in the placebo group vs.

60 events in the atorvastatin group]) by 36% (based on incidences of 1.9% for atorvastatin vs. 3.0% for placebo).

In a placebo-controlled study, the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin 10 mg on cardiovascular disease (CVD) endpoints was assessed in 2838 patients, 40-75 years old, with type 2 diabetes, one or more cardiovascular risk factors, LDL ≤160 mg/dL, and TG ≤600 mg/dL. Patients were followed for a median duration of 3.9 years. Atorvastatin 10 mg significantly ($p<0.05$) reduced: the rate of major cardiovascular events (MCVE) by 37%; the risk of stroke by 48%; and the risk of MI by 42%.

In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects with clinically evident CHD and an LDL-C level <130 mg/dL while receiving atorvastatin 10 mg. Patients were followed for a median duration of 4.9 years. Atorvastatin 80 mg significantly ($p\leq0.05$) reduced the rate of: MCVE by 22%; nonfatal, non-procedure related MI by 22%; fatal and non-fatal stroke by 25%; coronary revascularization by 28%; angina by 12%; and hospitalization for heart failure by 26%.

In a multicenter, double-blind, placebo-controlled, clinical study, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, patients with an acute coronary syndrome (non Q-wave MI or unstable angina) were randomized to receive atorvastatin 80 mg/day (n=1538) or placebo (n=1548). Treatment was initiated during the acute phase after hospital admission and lasted for a period of 16 weeks. Atorvastatin 80 mg/day provided a 16% ($p=0.048$) reduction in risk of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischemia requiring hospitalization. This was mainly due to a 26% reduction in re-hospitalization for angina pectoris with evidence of myocardial ischemia ($p=0.018$).

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 80 mg/day was compared to treatment with simvastatin 20-40 mg/day in 8,888 patients up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. In this prospective, randomized, open-label, blinded endpoint trial, patients, 76% of whom were on statin therapy at randomization, were followed for a median duration of 4.8 years. There was no significant difference between the treatment groups for the rate of first major coronary event (fatal CHD, nonfatal MI, and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin 80 mg/day group vs. 463 (10.4%) in the simvastatin 20-40 mg/day group or for all-cause mortality: 366 (8.2%) in the atorvastatin 80 mg/day group vs. 374 (8.4%) in the simvastatin 20-40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin 80 mg group and the simvastatin 20-40 mg group.

Homozygous Familial Hypercholesterolemia (HoFH)

A double-blind, randomized, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analyzed from a subgroup of patients (n=36) receiving atorvastatin 40 mg at baseline. Increasing the dose of atorvastatin from 40 to 80 mg (n=12) produced a reduction of LDL-C of 2% from baseline on atorvastatin 40 mg. Coadministered ezetimibe and atorvastatin equivalent to ATOZET (10/40 and 10/80 pooled, n=24), produced a reduction of LDL-C of 19% from baseline on atorvastatin 40 mg. In those patients coadministered ezetimibe and atorvastatin equivalent to ATOZET (10/80, n=12), a reduction of LDL-C of 25% from baseline on atorvastatin 40 mg was produced.

After completing the 12-week study, eligible patients (n=35), who were receiving atorvastatin 40 mg at baseline, were assigned to coadministered ezetimibe and atorvastatin equivalent to ATOZET 10/40 for up to an additional 24 months. Following at least 4 weeks of treatment, the atorvastatin dose could be doubled to a maximum dose of 80 mg. At the end of the 24 months, ATOZET (10/40 and 10/80 pooled) produced a reduction of LDL-C that was consistent with that seen in the 12-week study.

11. CLINICAL PHARMACOLOGY

11.1 Therapeutic Class

ATOZET (ezetimibe/atorvastatin) is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

11.2 Mechanism of Action

ATOZET

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. ATOZET contains ezetimibe and atorvastatin, two lipid-lowering compounds with complementary mechanisms of action. ATOZET reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.

Ezetimibe

Ezetimibe inhibits the intestinal absorption of cholesterol. 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 localizes 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 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo.

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

Atorvastatin

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.

11.3 Pharmacokinetics

General Introduction

ATOZET

ATOZET has been shown to be bioequivalent to coadministration of corresponding doses of ezetimibe and atorvastatin tablets.

Absorption

ATOZET

The effects of a high-fat meal on the pharmacokinetics of ezetimibe and atorvastatin when administered as ATOZET tablets are comparable to those reported for the individual tablets.

Ezetimibe

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.

Atorvastatin

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

Ezetimibe

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

Atorvastatin

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

Metabolism

Ezetimibe

Ezetimibe is metabolized 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.

Atorvastatin

Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. *In vitro*, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is

equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination

Ezetimibe

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 feces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Atorvastatin

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the medicinal product 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, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters MDR1 and BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Special Populations

Renal Impairment

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤ 30 ml/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9).

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

Atorvastatin

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

Hepatic Impairment

Ezetimibe

After a single 10-mg dose of ezetimibe, the mean area under the curve (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 *[see 4. WARNINGS AND PRECAUTIONS, 4.5 Hepatic Impairment]*.

Atorvastatin

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).

Pediatric

Ezetimibe

The pharmacokinetics of ezetimibe are similar between children ≥6 years and adults. Pharmacokinetic data in the pediatric population <6 years of age are not available.

Atorvastatin

Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in atorvastatin population PK model with data including pediatric HeFH patients (ages 10 years to 17 years of age, n=29) in an open-label, 8-week study.

Geriatric

Ezetimibe

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.

Atorvastatin

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.

Race

Based on a meta analysis of pharmacokinetic studies with ezetimibe, there were no pharmacokinetic differences between Blacks and Caucasians.

Gender

Ezetimibe

Plasma concentrations for total ezetimibe are slightly higher (<20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe.

Atorvastatin

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.

Hemodialysis

Atorvastatin

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

12. ANIMAL PHARMACOLOGY

The hypocholesterolemic effect of ezetimibe was evaluated in Rhesus monkeys, a model for the human metabolism of cholesterol, as well as in dogs. Rhesus monkeys were fed a cholesterol-containing diet that mimics a human Western diet. Ezetimibe was found to have an ED_{50} of 0.0005 mg/kg/day for inhibiting the rise in plasma cholesterol levels (ED_{100} = 0.003 mg/kg/day). The ED_{50} in dogs was found to be 0.007 mg/kg/day. These results are consistent with ezetimibe being an extremely potent cholesterol absorption inhibitor.

In dogs given ezetimibe (≥0.03 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 3-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a normal or cholesterol rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively. The relevance of these preclinical findings to humans is unknown.

13. ANIMAL TOXICOLOGY

13.1 Acute Toxicity

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.

13.2 Chronic Toxicity

ATOZET

The safety of concomitant administration of ezetimibe and atorvastatin was assessed in rats and dogs. When ezetimibe was coadministered with atorvastatin, simvastatin, pravastatin or lovastatin, for three months, toxicologic findings were consistent with those seen with statins administered alone.

Ezetimibe

Ezetimibe was well tolerated by mice, rats and dogs. No target organs of toxicity were identified in chronic studies at daily doses up to 1500 (males) and 500 mg/kg (females) in rats, up to 500 mg/kg in mice, or up to 300 mg/kg in dogs.

13.3 Carcinogenesis

Ezetimibe

In two-year studies conducted in mice and rats, ezetimibe was not carcinogenic.

Atorvastatin

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC_{0-24} value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC_{0-24} values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

13.4 Mutagenesis

ATOZET

Combination of ezetimibe with atorvastatin was not genotoxic in a series of *in vitro* and *in vivo* assays.

Ezetimibe

Ezetimibe was not genotoxic in a series of *in vivo* and *in vitro* tests.

Atorvastatin

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

13.5 Reproduction

Ezetimibe

Ezetimibe did not affect the fertility of male or female rats.

Atorvastatin

In female rats, atorvastatin at doses up to 225 mg/kg (56 times the human exposure) did not cause adverse effects on fertility. Studies in male rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80-mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

13.6 Development

ATOZET

Concomitant administration of ezetimibe and atorvastatin was not teratogenic in rats. In pregnant rabbits, a low incidence of skeletal malformations (fused sternebrae and fused caudal vertebrae) was observed when ezetimibe (1000 mg/kg; ≥146 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe) was administered with atorvastatin (5, 25, and 50 mg/kg). Exposure to the pharmacologically active form of atorvastatin was ≥1.4 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$.

Ezetimibe

Ezetimibe was not teratogenic in rats or rabbits and had no effect on prenatal or postnatal development.

Atorvastatin

Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

14. NAME OF THE DRUG

ATOZET® 10/10
(EZETIMIBE 10 MG/ATORVASTATIN 10 MG)
ATOZET® 10/20
(EZETIMIBE 10 MG/ATORVASTATIN 20 MG)
ATOZET® 10/40
(EZETIMIBE 10 MG/ATORVASTATIN 40 MG)
ATOZET® 10/80
(EZETIMIBE 10 MG/ATORVASTATIN 80 MG)

15. PHARMACEUTICAL FORM

Film-coated tablets

ATOZET 10 mg/10 mg: Capsule shaped, biconvex, white to off white tablets, with "257" debossed on one side of the tablet.

ATOZET 10 mg/20 mg: Capsule shaped, biconvex, white to off white tablets, with "333" debossed on one side of the tablet.

ATOZET 10 mg/40 mg: Capsule shaped, biconvex, white to off white tablets, with "337" debossed on one side of the tablet.

ATOZET 10 mg/80 mg: Capsule shaped, biconvex, white to off white tablets, with "357" debossed on one side of the tablet.

16. PHARMACEUTICAL PARTICULARS

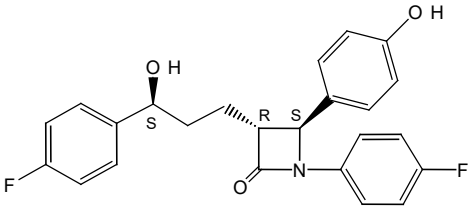
16.1 Chemistry

ATOZET contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

Ezetimibe

The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4.

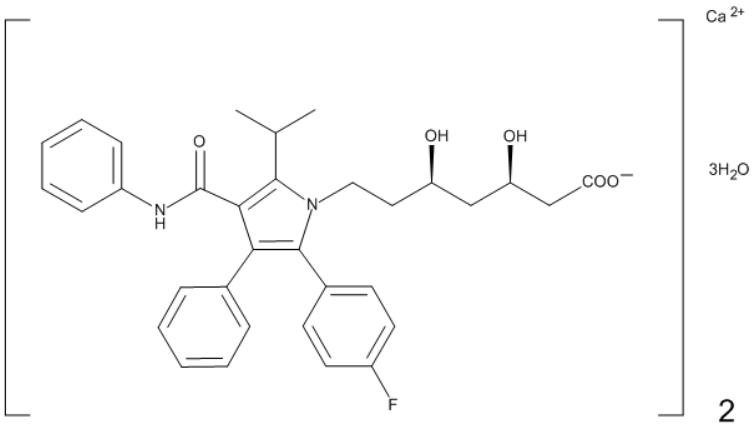
Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Its structural formula is:



Atorvastatin

Atorvastatin is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ,-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate, also known as Atorvastatin Calcium (crystalline trihydrate).

Atorvastatin calcium is a white or almost white powder that is soluble in dimethyl sulfoxide. The degree of solubility in water, ethanol, and methylene chloride is very slightly soluble to practically insoluble. The molecular formula of atorvastatin calcium is $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$. The molecular weight of atorvastatin calcium is 1209.36. Its structural formula is:



16.2 Composition

Active Ingredients

ATOZET is available for oral use as tablets containing 10 mg of ezetimibe and: 10.9 mg of atorvastatin calcium, equivalent to 10 mg of atorvastatin (ATOZET 10 mg/10 mg); 21.7 mg of atorvastatin calcium, equivalent to 20 mg of atorvastatin (ATOZET 10 mg/20 mg); 43.4 mg of atorvastatin calcium, equivalent to 40 mg of atorvastatin (ATOZET 10 mg/40 mg); or 86.8 mg of atorvastatin calcium, equivalent to 80 mg of atorvastatin (ATOZET 10 mg/80 mg).

Inactive Ingredients (List of excipients)

Each film-coated tablet of ATOZET contains the following inactive ingredients: calcium carbonate, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate, povidone, and sodium lauryl sulfate.

The film coating contains: hydroxypropyl methylcellulose/hypromellose, macrogol/polyethylene glycol, titanium dioxide, and talc.

16.3 Storage

Store up to 30°C.

16.4 Shelf Life

Please refer to expiry date on the outer carton.

16.5 Availability

ATOZET Tablet 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg are available in cartons of 30’s.

Not all presentations may be available locally.

16.6 Manufacturer

MSD International GmbH (Puerto Rico Branch) LLC
PRIDCO Industrial Park
State Road 183,
Las Piedras, Puerto Rico 00771

This package insert was last revised in March 2023.

ORGANON