ATOZET®

(Ezetimibe/Atorvastatin Tablet)

1. INDICATIONS AND USAGE

Primary Hypercholesterolemia

ATOZET is indicated as adjunctive therapy to diet for the reduction of elevated 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) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

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 10/40 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.

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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. The 10/80 mg dose of ATOZET is not locally available.

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 4. WARNINGS AND PRECAUTIONS, 4.4 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, 4.5 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.
- Pregnancy and nursing [*see 6. USE IN SPECIFIC POPULATIONS, 6.1. Pregnancy and 6.2. Nursing Mothers*].
- Atozet is contraindicated in patients with myopathy secondary to other lipid lowering agents
- Atozet in combination with fenofibrate is contraindicated in patients with gall bladder disease
- Atozet is contraindicated in concomitant use with fusidic acid.

4. WARNINGS AND PRECAUTIONS

4.1 Myopathy/Rhabdomyolysis

Ezetimibe

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone). However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. In clinical trials, the incidence of CPK > 10 X ULN was 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.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis.

Atorvastatin

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*].

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 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.

Liver function tests should be performed before the initiation of treatment and periodically thereafter. 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*].

4.3 Endocrine Function

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

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.

4.4 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.

4.5 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 give 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.

The co-administration of ezetimibe with fibrates, other than fenofibrate, has not been studied. Therefore, co-administration of ATOZET and fibrates is not recommended.
Fenofibrate
Fibrates may increase cholesterol excretion from the bile, and ezetimibe increased cholesterol in the gallbladder bile in a preclinical study in dogs. Given the potential for cholelithiasis, and the numerically higher incidence of cholecystectomies in patients administered ezetimibe and fenofibrate in a clinical study, co-administration of ATOZET and fenofibrate is not recommended in patients with pre-existing gallbladder disease.

4.6 Cyclosporine

In patients taking cyclosporine, therapy with ATOZET should be avoided.

4.7 Haemorrhagic Stroke

A post-hoc analysis of a clinical study (SPARCL) in patients without known coronary heart disease who had a recent stroke or TIA, showed a higher incidence of haemorrhagic stroke in patients on atorvastatin 80 mg (55/2365, 2.3%) compared to placebo (33/2366, 1.4%), (p=0.02). Throughout the study, all cause mortality was numerically higher in the atorvastatin arm than the placebo arm. At study end all cause mortality was 9.1% on atorvastatin vs. 8.9 % on placebo.
The increased risk of haemorrhagic stroke was observed in patients who entered the study with prior haemorrhagic stroke (15.6% for atorvastatin vs. 4.2 % for placebo, HR 4.06; 95% CI 0.84-19.57) or prior lacunar infarct (2.8% for atorvastatin vs. 0.6% for placebo, HR 4.99; 95%CI 1.71-14.61). All

cause mortality was also increased in these patients with prior haemorrhagic stroke (15.6% for atorvastatin vs. 10.4% for placebo) or prior lacunar infarct (10.9% for atorvastatin vs. 9.1% for placebo). The potential risk of haemorrhagic stroke should be carefully considered before initiating treatment with ATOZET in patients with recent (1-6 months) stroke or TIA.

In 68% of patients who entered the study with neither a haemorrhagic stroke nor lacunar infarct, the risk of haemorrhagic stroke on atorvastatin vs. placebo was 2% vs. 1.8 % (large vessel), 1.7% vs. 1.6 % (TIA), 1.6% vs. 1.7 % (unknown cause).

4.8 Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (*see 8. ADVERSE REACTIONS*). 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, ATOZET therapy should be discontinued.

4.9 Effect on Ubiquinone Levels (COQ_{10})

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term, statin-induced deficiency of ubiquinone has not been established.

4.10 Effect on Lipoprotein (a)

Like other HMG-CoA reductase inhibitors, atorvastatin has variable effects on lipoprotein (a) (Lp (a)). It is unclear whether the beneficial effects of lowering LDL-C and total cholesterol in some patients may be blunted by raised Lp (a) levels.

4.11 Effect on Laboratory Tests

ATOZET can cause elevations in ALT/AST, alkaline phosphatase, GGT, bilirubin and creatine kinase.

4.12 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.

4.13 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*].

4.14 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.

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 Co-A 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*]:

Erythromycin/Clarithromycin: In healthy individuals, co-administration of atorvastatin (10mg QD) and erythromycin (500mg QID), or clarithromycin (500mg BID), known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin. In patients taking clarithromycin the dose of ATOZET should not exceed 10/20 mg (*see 4. WARNINGS AND PRECAUTIONS*).

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 2. DOSAGE AND ADMINISTRATION, 2.8 Cyclosporine, Clarithromycin, Itraconazole, or Certain HIV/HCV Antiviral Agents and 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis*].

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 2. DOSAGE AND ADMINISTRATION*, *2.8 Cyclosporine, Clarithromycin, Itraconazole, or Certain HIV/HCV Antiviral Agents and 4. WARNINGS AND PRECAUTIONS, 4.1 Myopathy/Rhabdomyolysis*]. 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.

Diltiazem Hydrochloride: Co-administration of atorvastatin (40mg) with diltiazem (240mg) was associated with higher plasma concentrations of atorvastatin.

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).

Atorvastatin

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

Ezetimibe

Cimetidine: Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

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 m2) 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*].

5.3 Other Interactions

Antacids:

Ezetimibe

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.

Atorvastatin

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

Transporter Inhibitors

Atorvastatin

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporine) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10mg and cyclosporine 5.2mg/kg/day resulted in an increase in exposure to atorvastatin. The co-administration of ATOZET with cyclosporine should be avoided (*see 4. WARNINGS AND PRECAUTIONS* and *2. DOSAGE AND ADMINISTRATION*).

Ezetimibe

The effect of cyclosporine on ezetimibe was studied in eight post-renal transplant patients with creatinine clearance of >50 mL/min who were 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 group of historical healthy volunteers (n=17) who had taken a single 10-mg dose of ezetimibe alone.

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 dose 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*).

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, 4.5 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. 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, 4.13 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]*.

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.

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

Limited published data on atorvastatin from observational studies, meta-analyses and case reports have not shown an increased risk of major congenital malformations or miscarriage. 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.

In animal reproduction studies in rats and rabbits there was no evidence of embryo-fetal toxicity or congenital malformations at doses up to 30 and 20 times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 80 mg, based on body surface are (mg/m^2). In rats administered atorvastatin during gestation and lactation, decreased postnatal growth and development was observed at doses ≥ 6 times the MRHD.

6.2 Nursing Mothers

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 and atorvastatin are excreted in milk. It is not known whether ezetimibe is excreted into human breast 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 of 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:

	Uncommon	Common
Infections and Infestations:	Influenza	
Psychiatric disorders:	depression; insomnia; sleep disorder	
Nervous system disorders:	dizziness; dysgeusia; headache; paresthesia	
Cardiac disorders:	sinus bradycardia	
Vascular disorders:	hot flush	
Respiratory, thoracic and mediastinal disorders:	Dyspnea	
Gastrointestinal disorders:	abdominal discomfort; abdominal distension; abdominal pain; abdominal pain lower; abdominal pain upper; constipation; dyspepsia; flatulence; frequent bowel movements; gastritis; nausea; stomach discomfort	diarrhea
Skin and subcutaneous tissue disorders:	acne; urticaria	
Musculoskeletal and connective tissue disorders:	arthralgia; back pain; muscle fatigue; muscle spasms; muscular weakness; pain in extremity	myalgia
General disorders and administration site conditions:	asthenia; fatigue; malaise; edema	
Investigations:	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, 4.2 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

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

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

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; tendonopathy, 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>30kg/m^2, raised triglycerides, history of hypertension)

If there is any adverse events, please inform to PT Organon Pharma Indonesia Tbk, MSIG Tower Lt. 37, Jl. Jend. Sudirman Kav. 21, Jakarta 12920 Telp: (021) XXXXX

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 2.)

Table 2

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 3.) 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 ATOZET10/10 and atorvastatin 20 mg were 186 mg/dL and 187 mg/dL, respectively.

Table 3
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 4.) 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 4
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 ATOZET10/20 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.

ATOZET10/40 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 5.) 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 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 10/40	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 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 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 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 6.

Table 6
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 6 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%.

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 an 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 animals 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 14C-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.

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, 4.4 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 absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population < 10 years of age are not available. Clinical experience in pediatric and adolescent patients (ages 9 to 17) has been limited to patients with HoFH.

Atorvastatin

Pharmacokinetic studies have not been conducted in the pediatric population.

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 TOXICOLOGY

12.1 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.

12.2 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.

12.3 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.

12.4 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.

12.5 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 effect 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.

12.6 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).

Storage Condition:

Store below 30°C

Shelf life:

24 months

HARUS DENGAN RESEP DOKTER

Presentation:

ATOZET® 10/10 (Ezetimibe 10 mg/Atorvastatin 10 mg) film-coated tablet;

Reg. No. DKI1863501217A1

ATOZET® 10/20 (Ezetimibe 10 mg/ Atorvastatin 20 mg) film-coated tablet;

Reg. No. DKI1863501217B1

ATOZET® 10/40 (Ezetimibe 10 mg/ Atorvastatin 40 mg) film-coated tablet;

Reg. No. DKI1863501217C1

Manufactured by:

MSD International GmbH (Puerto Rico Branch) LLC,

Puerto Rico

Packed and released by:

Merck Sharp & Dohme BV,

Haarlem, Netherlands

Registered by:

PT Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

S-CCDS-MK0653C-T-122018

ORGANON

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INFORMASI MENGENAI ATOZET® (EZETIMIBE/ATORVASTATIN) UNTUK PASIEN

Bacalah lembar informasi ini dengan seksama sebelum anda mulai menggunakan obat, meskipun anda pernah menggunakan obat ini sebelumnya. Beberapa informasi dapat saja berubah. Anda sebaiknya juga membaca semua informasi tentang obat yang anda Minum saat ini.

Ingatlah bahwa dokter anda meresepkan obat ini hanya untuk anda. Jangan pernah memberikan obat anda kepada orang lain.

1. MENGAPA DOKTER SAYA MERESEPKAN ATOZET?

Dokter anda meresepkan ATOZET untuk mengurangi jumlah kolesterol dan trigliserida dalam darah anda. Kolesterol adalah salah satu dari beberapa substansi lemak yang didapatkan dalam aliran darah. Kolesterol total anda terutama terdiri dari kolesterol LDL dan HDL.

Kolesterol LDL sering juga disebut kolesterol “jahat” karena ia dapat membentuk plak dalam dinding pembuluh darah arteri anda. Pada akhirnya plak ini dapat menyebabkan arteri menjadi sempit. Penyempitan ini dapat memperlambat atau menyumbat aliran darah ke organ vital seperti jantung dan otak. Penyumbatan aliran darah ini dapat menyebabkan serangan jantung atau stroke.

Kolesterol HDL sering juga disebut kolesterol “baik” karena ia dapat mencegah kolesterol jahat menyumbat pembuluh darah arteri dan melindungi dari penyakit jantung. Trigliserida

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adalah bentuk lain dari lemak dalam darah anda yang dapat meningkatkan risiko anda untuk penyakit jantung.

Bagaimana cara mengobati kadar kolesterol yang tinggi?

Kadar kolesterol yang tinggi dapat diobati dengan dua cara utama:

Mengubah gaya hidup – seperti diet rendah kolesterol, meningkatkan aktivitas fisik dan tata laksana berat badan.

Obat – obat penurun kolesterol digunakan bersama dengan mengubah gaya hidup untuk membantu menurunkan kolesterol. Dokter anda meresepkan ATOZET untuk membantu menurunkan kolesterol anda.

2. BAGAIMANA CARA PENGGUNAAN ATOZET?

- Minumlah satu tablet ATOZET 10/10, 10/20 atau 10/40 per oral setiap hari, jam berapapun yang nyaman bagi anda.
- Minumlah ATOZET dengan atau tanpa makanan.
- Bila dokter anda meresepkan ATOZET bersama dengan kolestiramin (sekuestran asam empedu) atau sekuestran asam empedu lainnya, ATOZET sebaiknya diminum 2 jam sebelum atau 4 jam sesudah meminum sekuestran asam empedu.
- ATOZET sebaiknya digunakan sesuai instruksi dokter anda. Lanjutkan penggunaan obat penurun kolesterol kecuali dokter anda memberitahukan anda untuk menghentikannya.

2.1 Apakah yang sebaiknya saya lakukan bila terjadi overdosis?

Minum ATOZET sesuai resep yang diberikan untuk anda. Bila anda meminum ATOZET lebih banyak dari yang diresepkan, segera hubungi dokter atau apoteker anda.

2.2 Apakah yang sebaiknya saya lakukan bila saya terlupa satu dosis?

Usahakan meminum ATOZET sesuai resep. Akan tetapi bila anda terlupa satu dosis, mulailah kembali jadwal biasanya satu tablet sehari.

3. APAKAH YANG HARUS SAYA KETAHUI SEBELUM MENGGUNAKAN ATOZET?

Penting bagi anda untuk terus meminum ATOZET setiap hari sesuai resep yang diberikan oleh dokter anda.

Walaupun anda menggunakan obat untuk mengobati kadar kolesterol yang tinggi, penting bagi anda memeriksakan kadar kolesterol secara teratur. Anda sebaiknya mengetahui kadar kolesterol dan target capaiannya.

3.1 Siapakah yang tidak boleh menggunakan ATOZET?

Jangan menggunakan ATOZET bila anda:

- Hipersensitif (alergi) terhadap ezetimibe, atorvastatin, atau bahan lainnya yang terkandung dalam tablet ATOZET
- Memiliki penyakit hati aktif
- Hamil atau menyusui

3.2 Apakah yang sebaiknya saya beritahukan kepada dokter sebelum dan ketika menggunakan ATOZET?

- Masalah medis atau alergi: Beritahukan kepada dokter (apoteker) mengenai semua kondisi medis anda (termasuk penyakit hati atau masalah hati) yang anda sedang atau pernah dialami dan semua alergi.
- Alkohol: Beritahukan kepada dokter anda bila anda mengonsumsi alkohol dalam jumlah yang cukup banyak atau memiliki riwayat penyakit hati.

Anda dapat memperoleh informasi lebih lanjut dari dokter atau apoteker anda yang memiliki informasi lebih terinci.

3.3 Kehamilan

Jangan menggunakan ATOZET bila anda sedang hamil, berusaha untuk hamil atau menyangka sedang hamil. Bila anda hamil ketika menggunakan ATOZET, hentikan penggunaannya dan segera hubungi dokter anda.

3.4 Menyusui

Jangan menggunakan ATOZET bila anda sedang menyusui.

3.5 Anak

ATOZET tidak direkomendasikan untuk anak-anak.

3.6 Usia lanjut

Tidak ada perhatian khusus.

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3.7 Apakah saya dapat menggunakan ATOZET bersama dengan obat, suplemen diet, produk herbal atau makanan lainnya?

Beritahukan kepada dokter anda mengenai semua obat yang anda Minum atau anda rencanakan untuk menggunakannya, termasuk obat resep dan nonresep, vitamin dan suplemen herbal.

Sangat penting anda memberitahukan kepada dokter bila anda menggunakan berikut ini:

- Siklosporin (obat yang sering digunakan pada pasien transplantasi organ)
- Eritromisin, klaritromisin, asam fusidat atau rifampisin (obat untuk infeksi bakterial)
- Beberapa penghambat kanal kalsium yang digunakan untuk angina atau tekanan darah tinggi, contohnya amlodipin dan diltiazem
- Penghambat protease HIV (obat untuk AIDS)
- Kontrasepsi oral (obat untuk mencegah kehamilan)
- Antasida (obat saluran cerna yang mengandung aluminium atau magnesium)
- Simetidin (digunakan untuk rasa panas terbakar di dada dan luka lambung)
- Agen antivirus hepatitis C seperti boceprevir, telaprevir, elbasvir, atau grazoprevir (obat yang digunakan untuk mengobati infeksi virus hepatitis C)
- Obat-obatan seperti:
    - ketokonazol atau itrakonazol (obat untuk infeksi jamur)
    - fibrat, kolestipol, kolestiramin (obat untuk menurunkan kolesterol)
    - digoksin (obat untuk mengatur irama jantung anda)
    - warfarin atau fluindion (obat untuk mencegah penggumpalan darah)

3.8 Apakah saya dapat mengendarai atau mengoperasikan mesin ketika menggunakan ATOZET?

Terdapat laporan terjadinya efek samping ATOZET yang dapat memengaruhi kemampuan anda mengendarai atau mengoperasikan mesin. Respons individual terhadap ATOZET dapat bervariasi. (Lihat **Apakah efek tidak diinginkan yang dimiliki oleh ATOZET?**)

4. APAKAH EFEK TIDAK DIINGINKAN YANG DIMILIKI OLEH ATOZET?

Semua obat memiliki efek tidak diinginkan yang disebut efek samping.

Pada uji klinis, ATOZET umumnya dapat ditoleransi baik. Efek samping yang terjadi biasanya ringan, sementara dan hampir sama dengan tipe dan frekuensi efek samping pada pasien yang diberikan ezetimibe tunggal atau atorvastatin tunggal.

Berikut ini adalah laporan efek samping yang sering terjadi: diare dan nyeri otot.

Berikut ini adalah laporan efek samping yang tidak sering terjadi: flu; depresi; kesulitan tidur; gangguan tidur; pusing; sakit kepala; gangguan pengecap; kesemutan; denyut jantung lambat; *hot flush*; sesak napas, rasa tidak nyaman, kembung, nyeri (termasuk perut atas dan bawah) di perut; konstipasi; pencernaan; flatulens; gerak usus berlebihan; radang lambung; mual; rasa tidak nyaman pada lambung; jerawat; bentol-bentol (biduran); nyeri sendi; lelah, kaku atau lemah otot; nyeri pada anggota tubuh; lemas yang tidak biasa; secara umum merasa tidak sehat; penumpukan cairan; Bengkak terutama di pergelangan kaki (edema); peningkatan fungsi hati atau otot pada tes darah; peningkatan berat badan.

Disamping itu, efek samping berikut ini dilaporkan terjadi pada pasien yang menggunakan tablet ATOZET atau ezetimibe atau atorvastatin:

- Reaksi alergi seperti bengkak wajah, bibir, lidah dan/atau tenggorok yang dapat menyebabkan kesulitan bernapas atau menelan (yang membutuhkan pengobatan segera), ruam dan bentol; ruam merah yang membengkak, kadang disertai lesi berbentuk target; Penyakit serius dengan pengelupasan dan pembengkakan kulit yang parah, pelepuhan kulit, mulut, mata, alat kelamin dan demam; Ruam kulit dengan bercak merah muda merah terutama di telapak tangan atau telapak kaki, yang mungkin melepuh; pendarahan tak terduga atau memar; cedera tendon; nyeri atau lemah otot (pada kasus yang sangat jarang terjadi tidak hilang setelah menghentikan ATOZET); lelah yang tidak biasa; perubahan pada beberapa tes laboratorium darah dan urin; masalah hati; radang pankreas; batu kandung empedu; radang kandung empedu; muntah; batuk; rasa panas terbakar di dada; nyeri leher; penurunan nafsu makan; hilang nafsu makan; nyeri dada; nyeri; tekanan darah tinggi; radang saluran hidung; nyeri tenggorok; perdarahan hidung; mimpi buruk; penurunan sensasi terhadap nyeri atau sentuhan; mulut kering; hilang ingatan; bingung; dering di dalam telinga dan/atau kepala, bersendawa; ruam kulit dan gatal-gatal; rambut rontok; demam; penglihatan kabur; gangguan penglihatan; gangguan pendengaran; ginekomastia (pembesaran payudara pada pria dan wanita).

Efek samping berikut telah dilaporkan dengan beberapa statin (obat-obatan dengan jenis yang sama):

- Kesulitan seksual
- depresi

- Masalah pernapasan termasuk batuk terus-menerus dan / atau sesak napas atau demam
- Diabetes (ini lebih mungkin terjadi jika Anda memiliki kadar gula dan lemak dalam darah tinggi, kelebihan berat badan dan memiliki tekanan darah tinggi. Dokter akan memonitor Anda saat meminum obat ini.)

Segera hubungi dokter bila anda mengalami nyeri atau lemah otot yang tidak jelas dan terutama, jika pada saat bersamaan, Anda merasa tidak sehat atau memiliki suhu tinggi, ketika anda menggunakan ATOZET atau setelah dokter Anda menyarankan Anda untuk berhenti minum Atozet. Hal ini karena pada kesempatan yang jarang terjadi, masalah otot dapat serius hingga terjadi perusakan otot yang mengakibatkan kerusakan ginjal.

Bicaralah kepada dokter kapanpun anda memiliki masalah kesehatan yang anda pikir mungkin terkait dengan ATOZET.

Bila anda diberi resep ATOZET, dokter anda sebaiknya melakukan tes darah untuk memeriksa hati anda sebelum anda mulai menggunakan ATOZET dan bila anda memiliki gejala gangguan hati ketika anda menggunakan ATOZET. Hubungi dokter anda segera bila anda memiliki gejala gangguan hati berikut ini:

- Merasa lelah atau lemah
- Hilang nafsu makan
- Nyeri perut atas
- Urin berwarna gelap
- Kulit atau bagian putih dari mata anda menjadi kekuningan

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Tanyakan kepada dokter atau apoteker anda untuk informasi lebih lanjut. Mereka memiliki daftar efek samping yang lebih lengkap. Beritahukan kepada dokter [atau apoteker] anda segera mengenai hal ini atau gejala lainnya yang tidak biasa.

5. APAKAH ATOZET?

ATOZET (ezetimibe/atorvastatin) adalah tablet bersalut selaput yang tersedia dalam empat kekuatan:

- 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)

Disamping itu, ATOZET mengandung bahan tidak aktif : kalsium karbonat, koloidal silikon dioksida, natrium kroskarmelose, hidroksipropil selulosa, laktosa monohidtrat, magnesium stearat, mikrokristalin selulosa, polisorbat 80, povidon dan natrium lauril sulfat. Salut selaput mengandung: HPMC 29/10 / hipromelosa, makrogol / PEG, titanium dioksida dan talk.

ATOZET adalah obat yang digunakan untuk menurunkan kadar kolesterol total, kolesterol LDL (jahat) dan substansi lemak yang disebut trigliserida dalam darah. Disamping itu, ATOZET meningkatkan kadar kolesterol HDL (baik). Obat ini digunakan untuk pasien yang tidak dapat mengontrol kadar kolesterol mereka dengan cara diet saja. Anda sebaiknya tetap melaksanakan diet rendah kolesterol ketika menggunakan obat ini.

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ATOZET bekerja menurunkan kolesterol anda melalui dua cara. Ia menurunkan kolesterol yang diserap dalam saluran cerna anda dan juga kolesterol yang dibuat oleh tubuh anda sendiri. ATOZET tidak membantu anda menurunkan berat badan.

6. BERAPA LAMA SAYA DAPAT MENYIMPAN OBAT SAYA?

Jangan gunakan obat ini setelah tanggal pada keterangan setelah kata Exp. Date pada kemasan.

7. BAGAIMANA CARA MENYIMPAN ATOZET?

Simpanlah ATOZET dan semua obat dengan aman jauh dari jangkauan anak-anak. Simpanlah pada suhu di bawah 30°C.

8. BAGAIMANA BILA SAYA INGIN MENGETAHUI LEBIH BANYAK TENTANG ATOZET DAN KONDISI SAYA?

Anda dapat memperoleh informasi lebih lanjut dari dokter atau apoteker anda.

HARUS DENGAN RESEP DOKTER

ATOZET® 10/10 (Ezetimibe 10 mg/Atorvastatin 10 mg) film-coated tablet;
Reg. No. DKI1863501217A1
ATOZET® 10/20 (Ezetimibe 10 mg/ Atorvastatin 20 mg) film-coated tablet;
Reg. No. DKI1863501217B1
ATOZET® 10/40 (Ezetimibe 10 mg/ Atorvastatin 40 mg) film-coated tablet;
Reg. No. DKI1863501217C1

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Pendaftar:

PT. Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

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