HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LIPTRUZET safely and effectively. See full prescribing information for LIPTRUZET.

LIPTRUZET® (ezetimibe and atorvastatin) tablets for oral use
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	10/2024
Dosage and Administration (2.1, 2.2, 2.3)	10/2024
Contraindications (4)	10/2024
Contraindications, Pregnancy and Lactation (4) Removed	10/2024
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5)	10/2024

----------INDICATIONS AND USAGE----------

LIPTRUZET is a combination of ezetimibe, a dietary cholesterol absorption inhibitor, and atorvastatin, an HMG-CoA reductase inhibitor (statin) indicated (1)

- As an adjunct to diet to reduce elevated low-density lipoprotein cholesterol (LDL C)
  - in adult patients with primary hyperlipidemia.
  - In adults with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other lipid-lowering therapies, or alone if such treatments are unavailable, to reduce elevated LDL-C in adults with homozygous familial hypercholesterolemia (HoFH)

Atorvastatin

Atorvastatin, when used as a component of LIPTRUZET, is indicated to reduce the risk of:

- Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD
- MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD
- Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD

---------- DOSAGE AND ADMINISTRATION ----------

- Take orally once daily at any time of the day with or without food (2.1).
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating LIPTRUZET, and adjust dosage if necessary (2.1).
- Administer LIPTRUZET at least 2 hours before or 4 hours after administration of a bile acid sequestrant (2.1)
- Recommended starting dosage is one tablet (containing 10 mg of ezetimibe and either 10 mg or 20 mg of atorvastatin) once daily (2.2).
- Recommended starting dosage is 10/40 mg once daily for patients requiring a greater than 50% reduction in LDL-C (2.2).
- The maximum dosage is 10/80 mg once daily (2.2).
- See full prescribing information for LIPTRUZET dosage modifications due to drug interactions (2.3).

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: (ezetimibe mg/atorvastatin mg): 10/10, 10/20, 10/40, 10/80. (3)

----------CONTRAINDICATIONS----------

- Acute liver failure or decompensated cirrhosis (4)
- Hypersensitivity to atorvastatin, ezetimibe, or any excipient of LIPTRUZET (4)

---------- WARNINGS AND PRECAUTIONS ----------

- *Myopathy and Rhabdomyolysis:* Risk factors include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs, and higher LIPTRUZET dosage. Discontinue LIPTRUZET if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Temporarily discontinue LIPTRUZET in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis. Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing LIPTRUZET dosage. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever (5.1)
- *Immune-Mediated Necrotizing Myopathy (IMNM):* Rare reports of IMNM, an autoimmune myopathy, have been reported with statin use. Discontinue LIPTRUZET if IMNM is suspected (5.2)
- *Hepatic Dysfunction*: Increases in serum transaminases have occurred, some persistent. Rare reports of fatal and non-fatal hepatic failure have occurred. Consider testing liver enzymes before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIPITRUZET (5.3)

---------- ADVERSE REACTIONS ----------

- Most common adverse reactions (incidence ≥2% and greater than placebo) are: increased ALT, increased AST, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Organon LLC, a subsidiary of Organon & Co., at 1-844-674-3200 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- See full prescribing information for details regarding concomitant use of LIPTRUZET with other drugs or grapefruit juice that increase the risk of myopathy and rhabdomyolysis (2.5, 7.1)
- *Cyclosporine:* Combination increases exposure of LIPTRUZET and cyclosporine. Cyclosporine concentrations should be monitored in patients taking LIPTRUZET concomitantly (7.1)
- *Fibrates:* Coadministration of LIPTRUZET with fibrates other than fenofibrate is not recommended until use in patients is adequately studied. If cholelithiasis is suspected in a patient receiving LIPTRUZET and fenofibrate, gallbladder studies are indicated, and alternative lipid lowering therapy should be considered (7.1)
- *Bile Acid Sequestrants*: Cholestyramine combination decreases exposure of LIPTRUZET (7.2)
- *Rifampin or Other Inducers of Cytochrome P450 3A4:* May reduce atorvastatin plasma concentrations. Administer simultaneously with LIPTRUZET (7.2)
- *Oral Contraceptives:* May increase plasma levels of norethindrone and ethinyl estradiol; consider this effect when selecting an oral contraceptive (7.3)
- *Digoxin:* May increase digoxin plasma levels; monitor patients appropriately (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: May cause fetal harm (8.1)
- Lactation: Breastfeeding not recommended during treatment with LIPTRUZET (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LIPTRUZET®

LIPTRUZET is a combination of atorvastatin and ezetimibe, indicated:

- As an adjunct to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C):
  - In adults with primary hyperlipidemia.
  - In adults with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other lipid-lowering therapies, or alone if such treatments are unavailable, to reduce elevated LDL-C in adults with homozygous familial hypercholesterolemia (HoFH).

Atorvastatin

Atorvastatin, when used as a component of LIPTRUZET, is indicated to reduce the risk of:

- Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD
- MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD
- Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD

2 DOSAGE AND ADMINISTRATION

Patients should swallow LIPTRUZET tablets whole. Tablets should not be crushed, dissolved, or chewed.

2.1 Important Dosage and Administration Information

- Take LIPTRUZET orally once daily at any time of the day with or without food.
- Assess LDL-C when clinically appropriate, as early as 4 weeks after initiating LIPTRUZET, and adjust the dosage if necessary.
- Administer LIPTRUZET at least 2 hours before or 4 hours after administration of a bile acid sequestrant *[see Drug Interactions (7.2)]*.
- Coadminister LIPTRUZET and rifampin simultaneously *[see Drug Interactions (7.2)]*.
- If as dose is missed, take the missed dose as soon as possible. Do not double the next dose.

2.2 Recommended Dosage in Adult Patients

- The recommended starting dosage of LIPTRUZET is one tablet (containing 10 mg of ezetimibe and either 10 mg or 20 mg of atorvastatin) once daily in adults with primary hyperlipidemia or HeFH.
- The recommended starting dosage of LIPTRUZET is 10/40 mg once daily for adults who require reduction in LDL-C greater than 50%.
- The recommended starting dosage of LIPTRUZET is 10/40 mg/day in adults with HoFH. LIPTRUZET 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 maximum dosage is 10/80 mg once daily.

2.3 Dosage Modifications Due to Drug Interactions

Concomitant use of LIPTRUZET with the following drugs requires dosage and administration modifications [*see Warnings and Precautions (5.1) and Drug Interactions (7.1)].*

Anti-Viral Medications

- In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed LIPTRUZET 10/20 mg once daily.
- In patients taking nelfinavir, do not exceed LIPTRUZET 10/40 mg once daily.

Select Azole Antifungals or Macrolide Antibiotics

- In patients taking clarithromycin or itraconazole, do not exceed LIPTRUZET 10/20 mg once daily.

For additional recommendations regarding concomitant use of LIPTRUZET with other anti-viral medications, azole antifungals or macrolide antibiotics, *see Drug Interactions (7.1).*

3 DOSAGE FORMS AND STRENGTHS

LIPTRUZET film-coated tablets:

- 10 mg/10 mg (ezetimibe 10 mg/atorvastatin 10 mg), white to off-white capsule-shaped, biconvex with code "257" on one side.
- 10 mg/20 mg (ezetimibe 10 mg/atorvastatin 20 mg), white to off-white capsule-shaped, biconvex with code "333" on one side.
- 10 mg/40 mg (ezetimibe 10 mg/atorvastatin 40 mg), white to off-white capsule-shaped, biconvex with code "337" on one side.
- 10 mg/80 mg (ezetimibe 10 mg/atorvastatin 80 mg), white to off-white capsule-shaped, biconvex with code "357" on one side.

4 CONTRAINDICATIONS

LIPTRUZET is contraindicated in patients with:

- Acute liver failure or decompensated cirrhosis *[see Warnings and Precautions (5.3)]*.
- A known hypersensitivity to atorvastatin, ezetimibe, or any of the excipients in LIPTRUZET. Hypersensitivity reactions including anaphylaxis, angioedema, angioneurotic edema, rash, urticaria, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

Atorvastatin

Atorvastatin may cause myopathy [muscle pain, tenderness, or weakness associated with elevated creatine kinase (CK)] and rhabdomyolysis. Acute kidney injury secondary to myoglobinuria and rare fatalities have occurred as a result of rhabdomyolysis in patients treated with statins, including atorvastatin.

Risk Factors for Myopathy

Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs (including other lipid-lowering therapies), and higher atorvastatin dosage [*see Drug Interactions (7.1) and Use in Specific Populations (8.5, 8.6)*].

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

Atorvastatin exposure may be increased by drug interactions due to inhibition of cytochrome P450 enzyme 3A4 (CYP3A4) and/or transporters [e.g., breast cancer resistant protein (BCRP), organic anion-transporting polypeptide (OATP1B1/OATP1B3) and P-glycoprotein (P-gp)], resulting in an increased risk of myopathy and rhabdomyolysis. Concomitant use of cyclosporine, gemfibrozil, tipranavir plus ritonavir, or glecaprevir plus pibrentasvir with atorvastatin is not recommended. Atorvastatin dosage modifications are recommended for patients taking certain anti-viral, azole antifungals, or macrolide antibiotic medications *[see Dosage and Administration (2.5)]*. Cases of myopathy/rhabdomyolysis have been reported with atorvastatin co-administered with lipid modifying doses (>1 gram/day) of niacin, fibrates, colchicine, and ledipasvir plus sofosbuvir. Consider if the benefit of use of these products outweighs the increased risk of myopathy and rhabdomyolysis *[see Drug Interactions (7.1)].*

Concomitant intake of large quantities, more than 1.2 liters daily, of grapefruit juice is not recommended in patients taking atorvastatin *[see Drug Interactions (7.1)].*

Discontinue atorvastatin if markedly elevated CK levels occur or if myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if atorvastatin is discontinued. Temporarily discontinue atorvastatin in patients experiencing an acute or serious condition at high risk of developing renal failure secondary to rhabdomyolysis (e.g., sepsis; shock; severe hypovolemia; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy).

Inform patients of the risk of myopathy and rhabdomyolysis when starting or increasing the atorvastatin dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Ezetimibe

Ezetimibe may cause myopathy [muscle pain, tenderness, or weakness associated with elevated creatine kinase (CK)] and rhabdomyolysis *[see Adverse Reactions (6.1)]*. In post-marketing reports, most patients who developed rhabdomyolysis were taking a statin or other agents known to be associated with an increased risk of rhabdomyolysis, such as fibrates. If myopathy is suspected, discontinue ezetimibe and other concomitant medications, as appropriate.

5.2 Immune-Mediated Necrotizing Myopathy

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use, including reports of recurrence when the same or a different statin was administered. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase that persist despite discontinuation of statin treatment; positive anti-HMG CoA reductase antibody; muscle biopsy showing necrotizing myopathy; and improvement with immunosuppressive agents. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required. Discontinue LIPTRUZET if IMNM is suspected.

5.3 Hepatic Dysfunction

Atorvastatin

Increases in serum transaminases have been reported with use of atorvastatin *[see Adverse Reactions (6.1)]*. In most cases, these changes appeared soon after initiation, were transient, were not accompanied by symptoms, and resolved or improved on continued therapy or after a brief interruption in therapy. Persistent increases to more than three times the ULN in serum transaminases have occurred in approximately 0.7% of patients receiving atorvastatin in clinical trials. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin.

Ezetimibe

Increases in serum transaminases have been reported with use of ezetimibe *[see Adverse Reactions (6.1)]*. In controlled clinical combination studies of ezetimibe initiated concurrently with a statin, the incidence of consecutive elevations (≥3 X ULN) in hepatic transaminase levels was 1.3% for patients treated with ezetimibe administered with statins and 0.4% for patients treated with statins alone. Perform liver enzyme testing as clinically indicated and consider withdrawal of ezetimibe if increases in ALT or AST ≥3 X ULN persist.

LIPTRUZET

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury *[see Use in Specific Populations (8.7)]*.

Consider liver enzyme testing before LIPTRUZET initiation and when clinically indicated thereafter. LIPTRUZET is contraindicated in patients with acute liver failure or decompensated cirrhosis *[see Contraindications (4*)]. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue LIPTRUZET.

5.4 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including atorvastatin. Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

5.5 Increased Risk of Hemorrhagic Stroke in Patients on Atorvastatin 80 mg with Recent Hemorrhagic Stroke

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial where 2365 subjects, without CHD who had a stroke or TIA within the preceding 6 months, were treated with atorvastatin 80 mg, a higher incidence of hemorrhagic stroke was seen in the atorvastatin 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin (38, 1.6%) group as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Myopathy and Rhabdomyolysis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Necrotizing Myopathy *[see Warnings and Precautions (5.2)]*
- Hepatic Dysfunction *[see Warnings and Precautions (5.3)]*
- Increases in HbA1c and Fasting Serum Glucose Levels *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

LIPTRUZET

In a placebo-controlled clinical trial of coadministered ezetimibe and atorvastatin, 628 patients (age range 18 to 86 years, 59% female, 87% White, 4% Black or African American, 2% Asian, 7% other races; 6% identified as Hispanic or Latino ethnicity) with a median treatment duration of 12 weeks, 6% of patients on ezetimibe/atorvastatin and 5% of patients on placebo discontinued due to adverse reactions.

The most common adverse reactions in the group treated with ezetimibe/atorvastatin that led to treatment discontinuation and occurred at a rate greater than placebo were:

- Myalgia (0.8%)
- Abdominal pain (0.8%)
- Increased hepatic enzymes (0.8%)

The most commonly reported adverse reactions (incidence ≥2% and greater than placebo) in this trial were: increased ALT (5%), increased AST (4%), and musculoskeletal pain (4%).

Coadministered ezetimibe and atorvastatin has been evaluated for safety in 2,403 patients in 7 clinical trials (one placebo-controlled trial and six active-controlled trials).

Table 1 summarizes the frequency of clinical adverse reactions reported in ≥2% of patients treated with ezetimibe/atorvastatin (n=255) and at an incidence greater than placebo.

Table 1*: Adverse Reactions Occurring in ≥2% of Patients Treated with Ezetimibe/Atorvastatin and at an Incidence Greater than Placebo

Adverse Reaction	Placebo (%) n=60	Ezetimibe 10 mg (%) n=65	Atorvastatin† (%) n=248	Ezetimibe/Atorvastatin† (%) n=255
ALT increased	0	0	2	5
AST increased	0	0	<1	4
Musculoskeletal pain	3	8	5	4
Abdominal pain	2	2	4	3
Nausea	0	2	5	3
Arthralgia	0	5	6	3
Hyperkalemia	0	0	<1	2
Bronchitis	0	2	2	2
Sinusitis	0	3	2	2
Hot flushes	0	0	<1	2
Dizziness	0	6	<1	2
Coughing	0	3	<1	2
Muscle weakness	0	2	0	2

* Placebo-controlled combination trial in which the active ingredients equivalent to LIPTRUZET were coadministered.
† All doses.

After completing the 12-week trial, eligible patients were assigned to coadministered ezetimibe 10 mg and atorvastatin (10 to 80 mg) or atorvastatin (10-80 mg/day) for an additional 48 weeks. The long-term coadministration of ezetimibe plus atorvastatin had an overall safety profile similar to that of atorvastatin alone.

Ezetimibe

In 10 double-blind, placebo-controlled clinical trials, 2,396 patients with primary hyperlipidemia (age range 9 to 86 years, 50% female, 90% White, 5% Black or African American, 2% Asian, 3% other races; 3% identified as Hispanic or Latino ethnicity) and elevated LDL-C were treated with ezetimibe 10 mg/day for a median treatment duration of 12 weeks (range 0 to 39 weeks).

Adverse reactions reported in ≥2% of patients treated with ezetimibe and at an incidence greater than placebo are shown in Table 2.

Table 2: Adverse Reactions Occurring in ≥2% of Patients Treated with Ezetimibe and at an Incidence Greater than Placebo

Adverse Reaction	Placebo (%) n=1,159	Ezetimibe 10 mg (%) n=2,396
Upper respiratory tract infection	2.5	4.3
Diarrhea	3.7	4.1
Arthralgia	2.2	3.0
Sinusitis	2.2	2.8
Pain in extremity	2.5	2.7
Fatigue	1.5	2.4
Influenza	1.5	2.0

Atorvastatin

In an atorvastatin placebo-controlled clinical trial database of 16,066 patients (8,755 atorvastatin vs. 7,311 placebo; age range 10 to 93 years, 39% female, 91% White, 3% Black or African American, 2% Asian, 4% other races) with a median treatment duration of 53 weeks, the most common adverse reactions in patients treated with atorvastatin that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

Table 3 summarizes adverse reactions reported in ≥2% and at a rate greater than placebo in patients treated with atorvastatin (n=8,755), from seventeen placebo-controlled trials.

Table 3: Adverse Reactions Occurring in >2% in Patients Treated with any dose of Atorvastatin and at an Incidence Greater than Placebo (% of patients)

Adverse Reaction*	Placebo n=7,311	Atorvastatin 10 mg n=3,908	Atorvastatin 20 mg n=188	Atorvastatin 40 mg n=604	Atorvastatin 80 mg n=4,055	Any dose of Atorvastatin n=8,755
Nasopharyngitis	8.2	12.9	5.3	7.0	4.2	8.3
Arthralgia	6.5	8.9	11.7	10.6	4.3	6.9
Diarrhea	6.3	7.3	6.4	14.1	5.2	6.8
Pain in extremity	5.9	8.5	3.7	9.3	3.1	6.0
Urinary tract infection	5.6	6.9	6.4	8.0	4.1	5.7
Dyspepsia	4.3	5.9	3.2	6.0	3.3	4.7
Nausea	3.5	3.7	3.7	7.1	3.8	4.0
Musculoskeletal pain	3.6	5.2	3.2	5.1	2.3	3.8
Muscle spasms	3.0	4.6	4.8	5.1	2.4	3.6
Myalgia	3.1	3.6	5.9	8.4	2.7	3.5
Insomnia	2.9	2.8	1.1	5.3	2.8	3.0
Pharyngolaryngeal pain	2.1	3.9	1.6	2.8	0.7	2.3
Nasopharyngitis	8.2	12.9	5.3	7.0	4.2	8.3

*Adverse Reaction >2% in any dose greater than placebo

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ezetimibe and/or atorvastatin. Because the reactions below are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ezetimibe

Blood and lymphatic system disorders: thrombocytopenia

Gastrointestinal disorders: pancreatitis, abdominal pain, nausea

General disorders: fatigue

Hepatobiliary disorders: elevations in liver transaminases, including elevations more than 5X ULN; hepatitis; cholelithiasis; cholecystitis

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

Musculoskeletal disorders: elevated creatine phosphokinase; myopathy/rhabdomyolysis

Nervous system disorders: dizziness; paresthesia; depression; headache

Skin and subcutaneous tissue disorders: erythema multiforme

Atorvastatin

Gastrointestinal Disorders: pancreatitis

General Disorders: fatigue

Hepatobiliary Disorders: fatal and non-fatal hepatic failure

Immune System Disorders: anaphylaxis

Injury: tendon rupture

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, myositis. There have been rare reports of immune-mediated necrotizing myopathy associated with statin use.

Nervous System Disorders: dizziness, peripheral neuropathy. There have been rare reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with the use of all statins. Cognitive impairment was generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks). There have been rare reports of new-onset or exacerbation of myasthenia gravis, including ocular myasthenia, and reports of recurrence when the same or a different statin was administered.

Psychiatric Disorders: depression

Respiratory Disorders: interstitial lung disease

Skin and Subcutaneous Tissue Disorders: angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis)

7 DRUG INTERACTIONS

7.1 Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with LIPTRUZET

LIPTRUZET is a combination of atorvastatin and ezetimibe. LIPTRUZET plasma levels can be significantly increased with concomitant administration of inhibitors of CYP3A4 and transporters. Table 4 includes a list of drugs that may increase exposure to LIPTRUZET and may increase the risk of myopathy and rhabdomyolysis when used concomitantly and instructions for preventing or managing them *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

Table 4: Drug Interactions that may Increase the Risk of Myopathy and Rhabdomyolysis with LIPTRUZET

Cyclosporine or Gemfibrozil	
Clinical Impact:	Atorvastatin and ezetimibe plasma levels were significantly increased with concomitant administration of LIPTRUZET and cyclosporine, an inhibitor of CYP3A4 and OATP1B1 *[see Clinical Pharmacology (12.3)]*. Gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with LIPTRUZET**.**
Intervention	Concomitant use of cyclosporine or gemfibrozil with LIPTRUZET is not recommended.
Anti-Viral Medications	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of LIPTRUZET with many anti-viral medications, which are inhibitors of CYP3A4 and/or transporters (e.g., BCRP, OATP1B1/1B3, P-gp, MRP2, and/or OAT2) *[see Clinical Pharmacology (12.3)]*. Cases of myopathy and rhabdomyolysis have been reported with concomitant use of ledipasvir plus sofosbuvir with LIPTRUZET.
Intervention	• Concomitant use of tipranavir plus ritonavir or glecaprevir plus pibrentasvir with LIPTRUZET should be avoided. • In patients taking lopinavir plus ritonavir, or simeprevir, consider the risk/benefit of concomitant use with atorvastatin. • In patients taking saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir or letermovir, do not exceed LIPITRUZET 10/20 mg.

	• In patients taking nelfinavir, do not exceed LIPTRUZET 10/40 mg *[see Dosage and Administration (2.5)]*. • Consider the risk/benefit of concomitant use of ledipasvir plus sofosbuvir with LIPTRUZET. • Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Tipranavir plus ritonavir, glecaprevir plus pibrentasvir, lopinavir plus ritonavir, simeprevir, saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, elbasvir plus grazoprevir, letermovir, nelfinavir, and ledipasvir plus sofosbuvir.
Select Azole Antifungals or Macrolide Antibiotics	
Clinical Impact:	Atorvastatin plasma levels were significantly increased with concomitant administration of LIPTRUZET with select azole antifungals or macrolide antibiotics, due to inhibition of CYP3A4 and/or transporters *[see Clinical Pharmacology (12.3)]*.
Intervention	In patients taking clarithromycin or itraconazole, do not exceed LIPTRUZET 10/20 mg *[see Dosage and Administration (2.5)]*. Consider the risk/benefit of concomitant use of other azole antifungals or macrolide antibiotics with LIPTRUZET. Monitor all patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Examples:	Erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, and voriconazole.
Niacin	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been observed with concomitant use of lipid modifying dosages of niacin (≥1 gram/day niacin) with LIPTRUZET.
Intervention	Consider if the benefit of using lipid modifying dosages of niacin concomitantly with LIPTRUZET outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Fibrates (other than Gemfibrozil)	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with LIPTRUZET.
Intervention	Consider if the benefit of using fibrates concomitantly with LIPTRUZET outweighs the increased risk of myopathy and rhabdomyolysis. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Colchicine	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have been reported with concomitant use of colchicine with LIPTRUZET.
Intervention	Consider the risk/benefit of concomitant use of colchicine with LIPTRUZET. If concomitant use is decided, monitor patients for signs and symptoms of myopathy particularly during initiation of therapy and during upward dose titration of either drug.
Grapefruit Juice	
Clinical Impact:	Grapefruit juice consumption, especially excessive consumption, more than 1.2 liters/daily, can raise the plasma levels of atorvastatin and may increase the risk of myopathy and rhabdomyolysis.
Intervention	Avoid intake of large quantities of grapefruit juice, more than 1.2 liters daily, when taking LIPTRUZET.

7.2 Drug Interactions that may Decrease Exposure to LIPTRUZET

Table 5 presents drug interactions that may decrease exposure to LIPTRUZET and instructions for preventing or managing them.

Table 5: Drug Interactions that may Decrease Exposure to LIPTRUZET

Bile Acid Sequestrants	
Clinical Impact:	Concomitant cholestyramine administration decreased the mean exposure of total ezetimibe. This may result in a reduction of efficacy *[see Clinical Pharmacology (12.3)]*.
Intervention:	In patients taking a bile acid sequestrant, administer LIPTRUZET at least 2 hours before or 4 hours after the bile acid sequestrant *[see Dosage and Administration (2)]*.
Rifampin or Other Inducers of Cytochrome P450 3A4	
Clinical Impact:	Concomitant administration of LIPTRUZET with rifampin, an inducer of cytochrome P450 3A4 and inhibitor of OATP1B1, can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, delayed administration of LIPTRUZET after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations
Intervention:	Administer LIPTRUZET and rifampin simultaneously.

7.3 LIPTRUZET Effects on Other Drugs

Table 6 presents LIPTRUZET's effect on other drugs and instructions for preventing or managing them.

Table 6: LIPTRUZET Effects on Other Drugs

Oral Contraceptives	
Clinical Impact:	Co-administration of LIPTRUZET and an oral contraceptive increased plasma concentrations of norethindrone and ethinyl estradiol *[see Clinical Pharmacology (12.3)].*
Intervention:	Consider this when selecting an oral contraceptive for patients taking LIPTRUZET.
Digoxin	
Clinical Impact:	When multiple doses of LIPTRUZET and digoxin were co-administered, steady state plasma digoxin concentrations increased *[see Clinical Pharmacology (12.3)]*.
Intervention:	Monitor patients taking digoxin appropriately.
Coumarin Anticoagulants	
Clinical Impact:	LIPTRUZET may potentiate the effect of coumarin anticoagulants and increase the INR.
Intervention:	In patients taking coumarin anticoagulants, obtain an INR before starting LIPTRUZET and frequently enough after initiation, dose titration, or discontinuation to ensure that no significant alteration in INR occurs. Once the INR is stable, monitor INR at regularly recommended intervals.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Discontinue LIPTRUZET when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient.

LIPTRUZET decreases synthesis of cholesterol and possibly the synthesis of other biologically active substances derived from cholesterol, LIPTRUZET may cause fetal harm when administered to a pregnant woman based on the mechanism of action *[see Clinical Pharmacology (12.1)]*. In addition, treatment of hyperlipidemia is not generally necessary during pregnancy. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hyperlipidemia for most patients.

Available data from case series and prospective and retrospective observational cohort studies over decades of use with statins in pregnant women have not identified a drug-associated risk of major congenital malformations. Published data from prospective and retrospective observational cohort studies with atorvastatin use in pregnant women are insufficient to determine if there is a drug-associated risk of miscarriage (see Data). In animal reproduction studies, no adverse developmental effects were observed in pregnant rats or rabbits orally administered atorvastatin at doses that resulted in up to 30 and 20 times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 80 mg, based on body surface area (mg/m^2). In rats administered atorvastatin during gestation and lactation, decreased postnatal growth and development delay were observed at doses ≥ 6 times the MRHD (*see Data).*

There are insufficient data on ezetimibe use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, no adverse developmental effects were observed in pregnant rats and rabbits orally administered ezetimibe during the period of organogenesis at doses that resulted in up to 10 and 150 times, respectively, the human exposure at the MRHD, based on AUC (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Atorvastatin

A Medicaid cohort linkage study of 1,152 statin-exposed pregnant women compared to 886,996 controls did not find a significant teratogenic effect from maternal use of statins in the first trimester of pregnancy, after adjusting for potential confounders – including maternal age, diabetes mellitus, hypertension, obesity, and alcohol and tobacco use – using propensity score-based methods. The relative risk of congenital malformations between the group with statin use and the group with no statin use in the first trimester was 1.07 (95% confidence interval 0.85 to 1.37) after controlling for confounders, particularly pre-existing diabetes mellitus. There were also no statistically significant increases in any of the organ-specific malformations assessed after accounting for confounders. In the majority of pregnancies, statin treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. Study limitations include reliance on physician coding to define the presence of a malformation, lack of control for certain confounders such as body mass index, use of prescription dispensing as verification for the use of a statin, and lack of information on non-live births.

Animal Data

Ezetimibe

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats (gestation days 6-15) and rabbits (gestation days 7-19), there was no evidence of maternal toxicity or embryolethal effects at the doses tested (250, 500, 1,000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1,000 mg/kg/day (~10 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1,000 mg/kg/day (150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). The animal-to-human exposure multiple for total ezetimibe at the no-observed effect level was 6 times for rat and 134 times for rabbit. Fetal exposure to ezetimibe (conjugated and unconjugated) was confirmed in subsequent placental transfer studies conducted using a maternal dose of 1,000 mg/kg/day. The fetal

maternal plasma exposure ratio (total ezetimibe) was 1.5 for rats on gestation day 20 and 0.03 for rabbits on gestation day 22.

The effect of ezetimibe on prenatal and postnatal development and maternal function was evaluated in pregnant rats at doses of 100, 300 or 1,000 mg/kg/day from gestation day 6 through lactation day 21. No maternal toxicity or adverse developmental outcomes were observed up to and including the highest dose tested (17 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe).

Multiple-dose studies of ezetimibe given in combination with statins in rats and rabbits during organogenesis resulted in higher ezetimibe and statin exposures. Reproductive findings occurred at lower doses in combination therapy compared to monotherapy.

Atorvastatin
Atorvastatin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively. 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 at the MRHD based on surface area (mg/m^2). In rats, the maternally toxic dose of 300 mg/kg resulted in increased post-implantation loss and decreased fetal body weight. At the maternally toxic doses of 50 and 100 mg/kg/day in rabbits, there was increased post-implantation loss, and at 100 mg/kg/day fetal body weights were decreased.

In a study in pregnant rats administer 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 20 (weaning), there was decreased survival at birth, postnatal day 4, weaning, and post-weaning in pups of mothers dosed with 225 mg/kg/day, a dose at which maternal toxicity was observed. Pup body weight was decreased through postnatal day 21 at 100 mg/kg/day and through postnatal day 91 at 225 mg/kg/day. Pup development was delayed (rotarod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human exposure at the MRHD, based on AUC.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma.

8.2 Lactation

Risk Summary
There is no information about the presence of atorvastatin or ezetimibe in human breast milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.

It is not known whether ezetimibe or atorvastatin is present in human milk, but it has been shown that another drug in the same class as atorvastatin passes into human milk and atorvastatin is present in rat milk. In rats, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma *[see Data]*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Statins, including LIPTRUZET, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant. Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action, advise patients that breastfeeding is not recommended during treatment with LIPTRUZET *[see Use in Specific Populations (8.2) and Clinical Pharmacology (12.1)]*.

Data
Ezetimibe was present in the milk of lactating rats. The pup to maternal plasma ratio for total ezetimibe was 0.5 on lactation day 12.

Following a single oral administration of 10 mg/kg of radioactive atorvastatin to lactating rats, the concentration of total radioactivity was determined. Atorvastatin and/or its metabolites were measured in the breast milk and pup plasma at a 2:1 ratio (milk:plasma).

8.4 Pediatric Use

LIPTRUZET
Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Of the patients who received ezetimibe coadministered with atorvastatin in clinical studies, 1166 were 65 and older (this included 291 who were 75 and older). The effectiveness and safety of LIPTRUZET were similar between these patients and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, LIPTRUZET should be prescribed with caution in the elderly. *[See Clinical Pharmacology (12.3).]*

In geriatric patients, no dosage adjustment of LIPTRUZET is necessary.

8.6 Renal Impairment

Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor all patients with renal impairment for development of myopathy. These patients merit closer monitoring for skeletal muscle effects *[see Warnings and Precautions (5.1)]*.

In patients with renal impairment, no dosage adjustment of LIPTRUZET is necessary.

8.7 Hepatic Impairment

LIPTRUZET is not recommended for use in patients with moderate to severe hepatic impairment (Child-Pugh B or C) due to the unknown effects of the increased exposure to ezetimibe. LIPTRUZET is contraindicated in patients with active liver failure or decompensated cirrhosis *[see Contraindications (4), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

LIPTRUZET
No specific treatment of overdosage with LIPTRUZET can be recommended. In the event of overdose, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

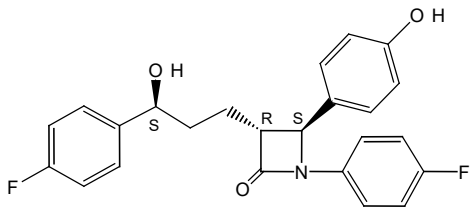
Atorvastatin
Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

11 DESCRIPTION

LIPTRUZET 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.

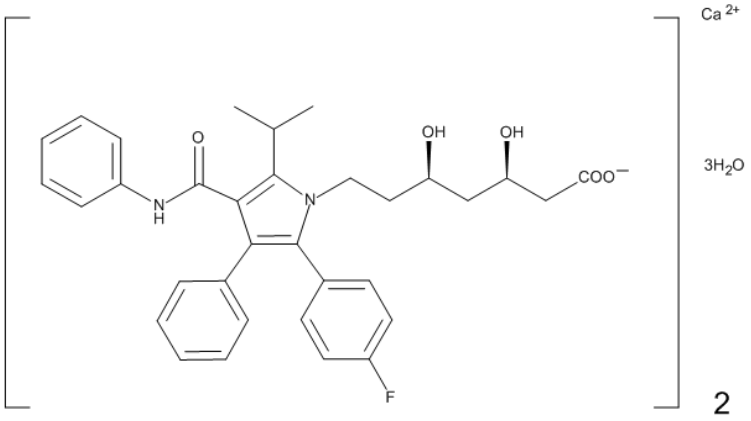
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4.

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 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.

Atorvastatin calcium is a white or almost white crystalline 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:



LIPTRUZET 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 (LIPTRUZET 10 mg/10 mg); 21.7 mg of atorvastatin calcium, equivalent to 20 mg of atorvastatin (LIPTRUZET 10 mg/20 mg); 43.4 mg of atorvastatin calcium, equivalent to 40 mg of atorvastatin (LIPTRUZET 10 mg/40 mg); or 86.8 mg of atorvastatin calcium, equivalent to 80 mg of atorvastatin (LIPTRUZET 10 mg/80 mg). Each film-coated tablet of LIPTRUZET contains the following inactive ingredients: calcium carbonate, croscarmellose sodium, colloidal silicon dioxide, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, polysorbate, and sodium lauryl sulfate. In addition, the film coating contains the following inactive ingredients: hydroxypropyl methylcellulose/hypromellose, macrogol/polyethylene glycol, titanium dioxide, and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LIPTRUZET

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. LIPTRUZET contains ezetimibe and atorvastatin, two lipid-lowering compounds.

Ezetimibe

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols.

Ezetimibe does not inhibit cholesterol synthesis in the liver or increase bile acid excretion. 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. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood.

Atorvastatin
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.

12.2 Pharmacodynamics
LIPTRUZET reduces total cholesterol (total C), LDL-C, apolipoprotein (Apo) B, and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with hyperlipidemia.

In a 2-week clinical study in 18 hypercholesterolemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54%, compared with placebo. Ezetimibe had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E and did not impair adrenocortical steroid hormone production (in a trial of 118 patients).

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response *[see Dosage and Administration (2)]*.

12.3 Pharmacokinetics
Absorption
Ezetimibe
After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide).
Atorvastatin
Maximum plasma atorvastatin concentrations after oral administration occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% 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. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Effect of Food

When LIPTRUZET 10/80 tablet was administered with a high-fat meal, atorvastatin C_{max} decreased by 7% and no effect on atorvastatin AUC was observed. A high-fat meal had no effect on the pharmacokinetics of unconjugated ezetimibe.

LIPTRUZET can be taken with or without food *[see Dosage and Administration (2.1)].*

Distribution
Ezetimibe
Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.

Atorvastatin
Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Elimination

Metabolism

Ezetimibe

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated.

In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. 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 eliminated from plasma with a half-life of approximately 22 hours for both ezetimibe and ezetimibe-glucuronide. Plasma concentration-time profiles exhibit multiple peaks, suggesting enterohepatic recycling.

Atorvastatin

Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *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. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this isozyme *[see Drug Interactions (7.1)]*. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Ezetimibe

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

Atorvastatin

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Specific Populations

Geriatric Patients

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥65 years) healthy subjects compared to younger subjects.

Atorvastatin

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults.

Pediatric Patients:

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.

Male and Female Patients

Ezetimibe

In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were slightly higher (<20%) in females than in males.

Atorvastatin

Plasma concentrations of atorvastatin in females differ from those in males (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between males and females.

Racial Groups

Ezetimibe

Based on a meta-analysis of multiple-dose pharmacokinetic studies, there were no pharmacokinetic differences between Black or African American and White subjects. Studies in Asian subjects indicated that the pharmacokinetics of ezetimibe were similar to those seen in White subjects**.**

Patients with Renal Impairment

[See Warnings and Precautions (5.1), Use in Specific Populations (8.6)]

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 values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Atorvastatin

Renal disease has no influence on the plasma concentrations or LDL-C reduction of 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.

Patients with Hepatic Impairment

Ezetimibe

After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6), compared to healthy subjects. The mean AUC values for total ezetimibe and ezetimibe increased approximately 3- to 4-fold and 5- to 6-fold, respectively, in patients with moderate (Child-Pugh score 7 to 9) or severe hepatic impairment (Child-Pugh score 10 to 15). In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic impairment, the mean AUC for total ezetimibe and ezetimibe increased approximately 4-fold on both Day 1 and Day 14 when compared to healthy subjects.

Atorvastatin

In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Child-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Child-Pugh B disease *[see Contraindications (4)]*.

Drug Interaction Studies

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with atorvastatin. Specific pharmacokinetic drug interaction studies with LIPTRUZET have not been performed.

Ezetimibe

Ezetimibe had no significant effect on a series of probe drugs (caffeine, dextromethorphan, tolbutamide, and IV midazolam) known to be metabolized by cytochrome P450 (1A2, 2D6, 2C8/9 and 3A4) in a “cocktail” study of twelve healthy adult males. This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes, and it is unlikely that ezetimibe will affect the metabolism of drugs that are metabolized by these enzymes.

Table 7: Effect of Coadministered Drugs on Total Ezetimibe

Coadministered Drug and Dosing Regimen	Total Ezetimibe*	
	Change in AUC	Change in C_{max}
Cyclosporine-stable dose required (75-150 mg BID)[†,‡]	↑240%	↑290%
Fenofibrate, 200 mg QD, 14 days[‡]	↑48%	↑64%
Gemfibrozil, 600 mg BID, 7 days[‡]	↑64%	↑91%
Cholestyramine, 4 g BID, 14 days[‡]	↓55%	↓4%
Aluminum & magnesium hydroxide combination antacid, single dose[§]	↓4%	↓30%
Cimetidine, 400 mg BID, 7 days	↑6%	↑22%
Glipizide, 10 mg, single dose	↑4%	↓8%
Statins		
Lovastatin 20 mg QD, 7 days	↑9%	↑3%
Pravastatin 20 mg QD, 14 days	↑7%	↑23%
Atorvastatin 10 mg QD, 14 days	↓2%	↑12%
Rosuvastatin 10 mg QD, 14 days	↑13%	↑18%
Fluvastatin 20 mg QD, 14 days	↓19%	↑7%

* Based on 10-mg dose of ezetimibe

† Post-renal transplant patients with mild impaired or normal renal function. In a different study, a renal transplant patient with severe renal impairment (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 healthy subjects.

‡ *See Drug Interactions (7)*

§ Supralox®, 20 mL

Table 8: Effect of Ezetimibe Coadministration on Systemic Exposure to Other Drugs

Coadministered Drug and its Dosage Regimen	Ezetimibe Dosage Regimen	Change in AUC of Coadministered Drug	Change in C_{max} of Coadministered Drug
Warfarin, 25 mg single dose on Day 7	10 mg QD, 11 days	↓2% (R-warfarin) ↓4% (S-warfarin)	↑3% (R-warfarin) ↑1% (S-warfarin)
Digoxin, 0.5 mg single dose	10 mg QD, 8 days	↑2%	↓7%
Gemfibrozil, 600 mg BID, 7 days*	10 mg QD, 7 days	↓1%	↓11%
Ethinyl estradiol & Levonorgestrel, QD, 21 days	10 mg QD, Days 8-14 of 21 d oral contraceptive cycle	Ethinyl estradiol 0% Levonorgestrel 0%	Ethinyl estradiol ↓9% Levonorgestrel ↓5%
Glipizide, 10 mg on Days 1 and 9	10 mg QD, Days 2-9	↓3%	↓5%
Fenofibrate, 200 mg QD, 14 days*	10 mg QD, 14 days	↑11%	↑7%
Cyclosporine, 100 mg single dose Day 7*	20 mg QD, 8 days	↑15%	↑10%
Statins			
Lovastatin 20 mg QD, 7 days	10 mg QD, 7 days	↑19%	↑3%
Pravastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓20%	↓24%
Atorvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↓4%	↑7%
Rosuvastatin 10 mg QD, 14 days	10 mg QD, 14 days	↑19%	↑17%
Fluvastatin 20 mg QD, 14 days	10 mg QD, 14 days	↓39%	↓27%

* *See Drug Interactions (7)*

Atorvastatin

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 transporter BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin.

Table 9: Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC[&]	Ratio of Cmax[&]
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD[a] for 28 days	8.69	10.66
[#]Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days	10 mg SD[c]	9.36	8.58
[#]Glecaprevir 400 mg QD[a]/pibrentasvir 120 mg QD[a], 7 days	10 mg QD[a] for 7 days	8.28	22.00
[#]Telaprevir 750 mg q8h[f], 10 days	20 mg SD[c]	7.88	10.60
[#,‡]Saquinavir 400 mg BID[b]/ritonavir 400 mg BID[b], 15 days	40 mg QD[a] for 4 days	3.93	4.31
[#]Elbasvir 50 mg QD[a]/grazoprevir 200 mg QD[a], 13 days	10 mg SD[c]	1.94	4.34
[#]Simeprevir 150 mg QD[a], 10 days	40 mg SD[c]	2.12	1.70
[#]Clarithromycin 500 mg BID[b], 9 days	80 mg QD[a] for 8 days	4.54	5.38
[#]Darunavir 300 mg BID[b]/ritonavir 100 mg BID[b], 9 days	10 mg QD[a] for 4 days	3.45	2.25
[#]Itraconazole 200 mg QD[a], 4 days	40 mg SD[c]	3.32	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	2.53	2.84
[#]Fosamprenavir 1400 mg BID[b], 14 days	10 mg QD[a] for 4 days	2.30	4.04
[#]Nelfinavir 1250 mg BID[b], 14 days	10 mg QD[a] for 28 days	1.74	2.22
[#]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	2.90
[#]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
Boceprevir 800 mg TID[d], 7 days	40 mg SD[c]	2.32	2.66

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

[#] See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (ratio of AUC up to 2.5) and/or Cmax (ratio of Cmax up to 1.71) have been reported with excessive grapefruit consumption (≥ 750 mL-1.2 liters per 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 plus 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 applied 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

Table 10: Effect of Atorvastatin on the Pharmacokinetics of Coadministered Drugs

Atorvastatin	Coadministered Drug and Dosing Regimen		
	Drug/Dose (mg)	Change in AUC	Change in C_{max}
80 mg QD[a] for 15 days	Antipyrine, 600 mg SD[c]	1.03	0.89
80 mg QD[a] for 10 days	*Digoxin 0.25 mg QD[a], 20 days	1.15	1.20
40 mg QD[a] for 22 days	Oral contraceptive QD[a], 2 months - norethindrone 1 mg - ethinyl estradiol 35 µg	 1.28 1.19	 1.23 1.30
10 mg SD[c]	Tipranavir 500 mg BID[b]/ritonavir 200 mg BID[b], 7 days	1.08	0.96
10 mg QD[a] for 4 days	Fosamprenavir 1400 mg BID[b], 14 days	0.73	0.82
10 mg QD[a] for 4 days	Fosamprenavir 700 mg BID[b]/ritonavir 100 mg BID[b], 14 days	0.99	0.94

* *See Drug Interactions (7)* for clinical significance.
[a] Once daily
[b] Twice daily
[c] Single dose

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal carcinogenicity or fertility studies have been conducted with the combination of ezetimibe and atorvastatin. The combination of ezetimibe with atorvastatin did not show evidence of mutagenicity *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with ezetimibe and atorvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 250 mg/kg with the combination of ezetimibe and atorvastatin (1:1) in the *in vivo* mouse micronucleus test.

Ezetimibe

A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (males) and 500 mg/kg/day (females) (~20 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity (Ames) test with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in human peripheral blood lymphocytes with or without metabolic activation. In addition, there was no evidence of genotoxicity in the *in vivo* mouse micronucleus test.

In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe).

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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ values of approximately 6 times the mean human plasma drug exposure after an 80-mg oral dose.

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.

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.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

In a multicenter, double-blind, placebo-controlled, clinical trial in adult 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, daily ezetimibe (10 mg), daily atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or coadministered ezetimibe and atorvastatin (10/10, 10/20, 10/40, and 10/80 mg/day) in the 12 week trial. After completing the 12 week trial, patients who agreed to participate in the study extension were assigned to coadministered ezetimibe (10 mg/day) and atorvastatin (10 to 80 mg/day) or atorvastatin (10 to80 mg/day) for an additional 48 weeks.

The patient population was: 59% female; 85% White, 6% Black or African American, 3% Asian, 1% American Indian, 5% other races; 18 to 86 years of age (mean age 57 years).

Patients receiving all doses of ezetimibe and atorvastatin were compared to those receiving all doses of atorvastatin. Ezetimibe plus atorvastatin lowered total-C, LDL-C, Apo B, TG, and non-HDL-C, and increased HDL-C significantly more than atorvastatin alone. (See Table 11.)

Table 11: Response to Ezetimibe/Atorvastatin in Patients with Primary Hyperlipidemia (Mean* % Change from Untreated Baseline† at 12 weeks)

Treatment (Daily Dose)	N	Total-C [Baseline§]	LDL-C [Baseline§]	Apo B [Baseline§]	TG* [Baseline§]	HDL-C [Baseline§]	Non-HDL-C [Baseline§]
Pooled data (All ezetimibe/ atorvastatin doses)‡	255	-41% [267]	-56% [182]	-45% [170]	-33% [165]	+7% [50.8]	-52% [217]
Pooled data (All atorvastatin doses)‡	248	-32% [269]	-44% [181]	-36% [168]	-24% [155]	+4% [53.7]	-41% [215]
Ezetimibe 10 mg	65	-14% [259]	-20% [177]	-15% [167]	-5% [145]	+4% [50.6]	-18% [209]
Placebo	60	+4% [262]	+4% [180]	+3% [168]	-6% [143]	+4% [50.4]	+4% [212]
Ezetimibe/Atorvastatin							
10/10	65	-38% [262]	-53% [177]	-43% [165]	-31% [158]	+9% [51.9]	-49% [211]
10/20	62	-39% [269]	-54% [184]	-44% [174]	-30% [165]	+9% [49.3]	-50% [220]
10/40	65	-42% [271]	-56% [184]	-45% [173]	-34% [180]	+5% [51.1]	-52% [220]
10/80	63	-46% [267]	-61% [183]	-50% [169]	-40% [146]	+7% [50.9]	-58% [216]
Atorvastatin							
10 mg	60	-26% [271]	-37% [185]	-28% [168]	-21% [153]	+6% [53.7]	-34% [217]
20 mg	60	-30% [267]	-42% [177]	-34% [164]	-23% [147]	+4% [55.5]	-39% [211]
40 mg	66	-32% [266]	-45% [180]	-37% [167]	-24% [159]	+4% [53.0]	-41% [213]
80 mg	62	-40% [270]	-54% [184]	-46% [171]	-31% [163]	+3% [52.7]	-51% [218]

* For triglycerides, median % change from baseline
† Baseline - on no lipid-lowering drug
‡ Ezetimibe/atorvastatinT pooled (10/10 to10/80) 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 to80 mg).
§ Baseline units: mg/dL; medians for TG, means for all other values

The changes in lipid endpoints after an additional 48 weeks of treatment with ezetimibe plus atorvastatin (all doses) or with atorvastatin (all doses) were generally consistent with the 12-week data displayed above in the 245 subjects (out of the 576 who completed the 12-week trial) who agreed to participate in the study extension.

A multicenter, double-blind, controlled, 14-week trial was conducted in 621 patients with 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 10 mg/day and atorvastatin 10 mg/day 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.

The patient population was: 47% female; 91% White, 2% Black or African American, 2% Asian, 5% other races identified as Hispanic or Latino ethnicity; 18 to 82 years of age (mean age 61 years).

Ezetimibe 10 mg/day plus atorvastatin 10 mg/day 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 12). In addition, at Week 4 significantly more patients receiving ezetimibe 10 mg/day plus atorvastatin 10 mg/day attained LDL-C <100 mg/dL (<2.6 mmol/L) compared to those receiving atorvastatin 20 mg, 12% vs. 2%. The baseline mean LDL-C levels for patients receiving ezetimibe 10 mg/day plus atorvastatin 10 mg/day and atorvastatin 20 mg were 186 mg/dL and 187 mg/dL, respectively.

Table 12: Response to Ezetimibe/Atorvastatin 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 [Baseline‡]	LDL-C [Baseline‡]	HDL-C [Baseline‡]	TG* [Baseline‡]	Non-HDL-C [Baseline‡]
Ezetimibe 10 mg plus Atorvastatin 10 mg	305	-17%§ [262]	-24%§ [186]	+2% [50.0]	-9%§ [117]	-22%§ [212]
Atorvastatin 20 mg	316	-6% [264]	-9% [187]	+1% [49.9]	-4% [119]	-8% [214]

* For triglycerides, median % change from baseline
† Patients on atorvastatin 10 mg, then switched to ezetimibe 10 mg plus atorvastatin 10 mg or titrated to atorvastatin 20 mg
‡ Baseline units: mg/dL; medians for TG, means for all other values
§ p<0.05 for difference with atorvastatin

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

The patient population was: 45% female; 60% White, 26% Multi-racial, 6% Black or African American, 8% Asian, <1% American Indian or Alaska native; 24 to 78 years of age (mean age 58 years).

Ezetimibe 10 mg/day plus atorvastatin 20 mg/day 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 13). In addition, significantly more patients receiving ezetimibe 10 mg/day plus atorvastatin 20 mg/day attained LDL-C <100 mg/dL compared to those receiving atorvastatin 40 mg, 84% vs. 49%.

Table 13: Response to Ezetimibe/Atorvastatin in Patients with Primary Hypercholesterolemia (Mean* % Change from Baseline†)

Treatment (Daily Dose)	N	Total-C [Baseline‡]	LDL-C [Baseline‡]	Apo B [Baseline‡]	HDL-C [Baseline‡]	TG* [Baseline‡]	Non-HDL-C [Baseline‡]
Ezetimibe 10 mg plus atorvastatin 20 mg	92	-20%§ [203]	-31%§ [120]	-21%§ [123]	+3% [50.9]	-18% [155]	-27%§ [152]
Atorvastatin 40 mg	92	-7% [201]	-11% [118]	-8% [120]	+1% [52.1]	-6% [148]	-10% [149]

* For triglycerides, median % change from baseline
† Patients on atorvastatin 20 mg, then switched to Ezetimibe 10 mg plus atorvastatin 20 mg or titrated to atorvastatin 40 mg
‡ Baseline units: mg/dL; medians for TG, means for all other values
§ 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) trial, a multicenter, double-blind, controlled, 6-week trial, included 556 patients with an LDL-C level ≥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 <70 mg/dL were randomized to receive either coadministered ezetimibe 10 mg/day and atorvastatin 40 mg/day or atorvastatin 80 mg for 6 weeks.

The patient population was: 39% female; 81% White, 11% Black or African American, 6% Multi-racial, 2% Asian; 31 to 80 years of age (mean age 52 years).

Ezetimibe 10 mg/day plus atorvastatin 40 mg/day 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 14). In addition, significantly more patients receiving ezetimibe 10 mg/day plus atorvastatin 40 mg/day attained LDL-C <70 mg/dL compared to those receiving atorvastatin 80 mg/day, 74% vs. 32%.

Table 14: Response to Ezetimibe/Atorvastatin in Patients with Primary Hypercholesterolemia (Mean* % Change from Baseline†)

Treatment (Daily Dose)	N	Total-C [Baseline‡]	LDL-C [Baseline‡]	Apo B [Baseline‡]	HDL-C [Baseline‡]	TG* [Baseline‡]	Non-HDL-C [Baseline‡]
Ezetimibe 10 mg plus atorvastatin 40 mg	277	-17%§ [165]	-27%§ [89]	-18%§ [101]	0% [47.7]	-12%§ [131]	-23%§ [117]
Atorvastatin 80 mg	279	-7% [165]	-11% [90]	-8% [102]	-1% [46.9]	-6% [136]	-9% [118]

* For triglycerides, median % change from baseline
† Patients on atorvastatin 20 mg, then switched to Ezetimibe 10 mg plus atorvastatin 40 mg or titrated to atorvastatin 80 mg
‡ Baseline units: mg/dL; medians for TG, means for all other values
§ p<0.05 for difference with atorvastatin

14.2 Homozygous Familial Hypercholesterolemia (HoFH)

A double-blind, randomized, 12-week trial 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/day at baseline. Increasing the dose of atorvastatin from 40 to 80 mg/day (n=12) produced a reduction of LDL-C of 2% from baseline on atorvastatin 40 mg. Coadministered ezetimibe 10 mg/day and atorvastatin 40 mg/day or 80 mg/day (pooled, n=24), produced a reduction of LDL-C of 19% from baseline on atorvastatin 40 mg/day. In those patients coadministered ezetimibe and atorvastatin (n=12), a reduction of LDL-C of 25% from baseline on atorvastatin 40 mg/day was produced.

After completing the 12-week study, eligible patients (n=35), who were receiving atorvastatin 40 mg/day at baseline, were assigned to coadministered ezetimibe 10 mg/day and atorvastatin 40 mg/day 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/day.

At the end of the 24 months, ezetimibe/atorvastatin(10/40 mg/day and 10/80 mg/day pooled) produced a reduction of LDL-C that was consistent with that seen in the 12-week trial.

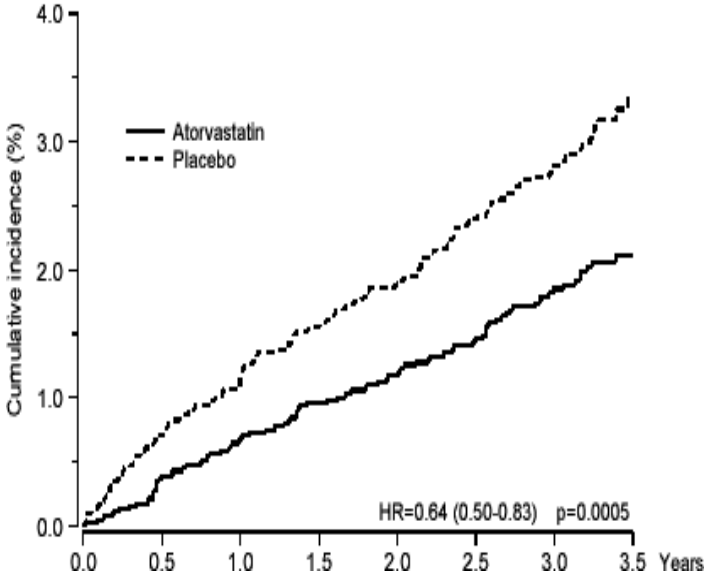
14.3 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 patients with hypertension, 40 to 80 years of age (mean of 63 years; 19% female; 95% White, 3% Black or African American, 1% South Asian, 1% other races), without a previous myocardial infarction and with total cholesterol (TC) levels ≤251 mg/dL. Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81%), age >55 years (85%), smoking (33%), diabetes (24%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14%), peripheral vascular disease (5%), left ventricular hypertrophy (14%), prior cerebrovascular event (10%), specific ECG abnormality (14%), proteinuria/albuminuria (62%). In this double-blind, placebo-controlled trial, patients were treated with anti-hypertensive therapy (goal BP <140/90 mm Hg for patients without diabetes; <130/80 mm Hg for patients with diabetes) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5,137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly 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 non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin was seen regardless of baseline LDL levels.

Figure 1: Effect of Atorvastatin 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42% (incidences of 1.4% for atorvastatin and 2.5% for placebo). Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or non-cardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on cardiovascular disease (CVD) endpoints was assessed in 2,838 subjects (94% White, 2% Black or African American, 2% South Asian, 1% other races; 68% male), ages 40 to 75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤160 mg/dL and triglycerides (TG) ≤600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the trial. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either atorvastatin 10 mg daily (1,429) or placebo (1,411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA1c 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

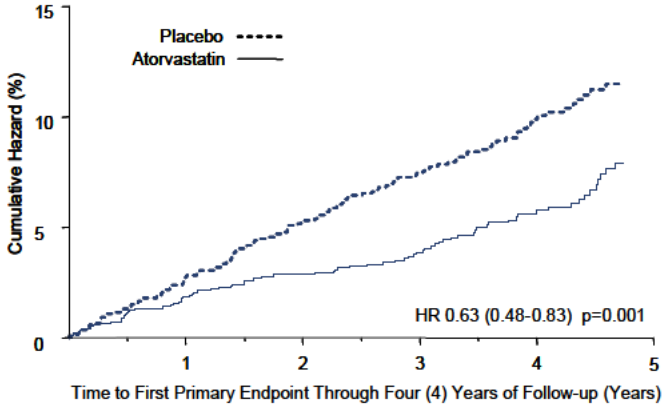
Atorvastatin significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 2). An effect of atorvastatin was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin significantly reduced the risk of stroke by 48% (21 events in the atorvastatin group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin group vs. 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86)

(p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the atorvastatin group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

Figure 2: Effect of Atorvastatin 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



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 (94% White, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non- HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin.

Treatment with atorvastatin 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p=0.0002 (see Figure 3 and Table 15). The overall risk reduction was consistent regardless of age (<65, ≥65) or sex.

Figure 3: Effect of Atorvastatin 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

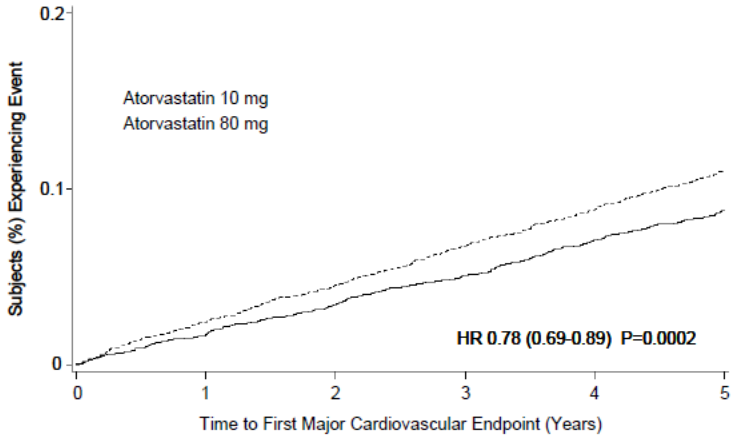


Table 15: Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5,006)		Atorvastatin 80 mg (N=4,995)		HR[a] (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Non-cardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

[a] atorvastatin 80 mg: atorvastatin 10 mg

[b] Component of other secondary endpoints

* Secondary endpoints not included in primary endpoint

HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin 80 mg/day significantly reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 15). Of the predefined secondary endpoints, treatment with atorvastatin 80 mg/day significantly reduced the rate of coronary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 15). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group. The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group.

16 HOW SUPPLIED/STORAGE AND HANDLING

LIPTRUZET tablets are supplied as follows:

Strength	How Supplied	NDC	Tablet Description
10/10 mg	unit of use packages of 30 (one carton containing one multi-	NDC-pending	white to off-white capsule-shaped, biconvex film-coated

	fold wallet with two 15-count blister cards)		tablets with code “257” on one side.
	unit of use packages of 90 (three cartons each containing one multi-fold wallet with two 15-count blister cards)	NDC-pending	
10/20 mg	unit of use packages of 30 (one carton containing one multi-fold wallet with two 15-count blister cards)	NDC-pending	white to off-white capsule-shaped, biconvex film-coated tablets with code “333” on one side.
	unit of use packages of 90 (three cartons each containing one multi-fold wallet with two 15-count blister cards)	NDC-pending	
10/40 mg	unit of use packages of 30 (one carton containing one multi-fold wallet with two 15-count blister cards)	NDC-pending	white to off-white capsule-shaped, biconvex film-coated tablets with code “337” on one side.
	unit of use packages of 90 (three cartons each containing one multi-fold wallet with two 15-count blister cards)	NDC-pending	
10/80 mg	unit of use packages of 30 (one carton containing one multi-fold wallet with two 15-count blister cards)	NDC-pending	white to off-white capsule-shaped, biconvex film-coated tablets with code “357” on one side.
	unit of use packages of 90 (three cartons each containing one multi-fold wallet with two 15-count blister cards)	NDC-pending	

Storage

Store LIPTRUZET at 68 to 77°F (20 to 25°C), excursions permitted between 59 to 86°F (between 15 to 30°C) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved Patient Labeling (Patient Information).

Myopathy and Rhabdomyolysis

Advise patients that LIPTRUZET may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication or consuming large quantities of grapefruit juice and they should discuss all medication, both prescription and over the counter, with their healthcare provider. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever *[see Warnings and Precautions (5.1), Drug Interactions (7.1)]*.

Hepatic Dysfunction

Inform patients that LIPTRUZET may cause liver enzyme elevations and possibly liver failure. Advise patients to promptly report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice [see Warnings and Precautions (5.3)].

Increases in HbA1c and Fasting Serum Glucose Levels

Inform patients that increases in HbA1c and fasting serum glucose levels may occur with LIPTRUZET. Encourage patients to optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices *[see Warnings and Precautions (5.4)].*

Pregnancy

Advise pregnant patients and patients who can become pregnant of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy to discuss if LIPTRUZET should be discontinued *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with LIPTRUZET *[see Use in Specific Populations (8.2)]*.

Missed Dose

Instruct patients to take LIPTRUZET only as prescribed. If a dose is missed, it should be taken as soon as possible. Advise patients not to double their next dose.

Organon LLC, a subsidiary of
ORGANON & Co.,
Jersey City, NJ 07302, USA

For patent information: www.organon.com/our-solutions/patent/

uspi-og0653c-cft-XXXXrXXX

PATIENT INFORMATION
LIPTRUZET® [LIP-true-zett]
(ezetimibe and atorvastatin)
tablets, for oral use

Read this information carefully before you start taking LIPTRUZET and each time you get a refill. If you have any questions about LIPTRUZET, ask your healthcare provider. Only your healthcare provider can determine if LIPTRUZET is right for you.

What is LIPTRUZET?

LIPTRUZET is a prescription medicine that contains the cholesterol lowering medicines, atorvastatin and ezetimibe.

- LIPTRUZET is used along with diet to reduce low density lipoprotein cholesterol (LDL-C) or "bad" cholesterol in adults with:
  - primary hyperlipidemia.
  - heterozygous familial hypercholesterolemia (HeFH) (An inherited condition that causes high levels of LDL-C).

- LIPTRUZET is used along with other cholesterol lowering treatments or alone if such treatments are unavailable in adults with homozygous familial hypercholesterolemia (HoFH) (an inherited condition that causes high levels of LDL-C).

- Atorvastatin when used as a component of LIPTRUZET is used to reduce the risk of:
  - heart attack, stroke, the need for procedures to improve blood flow to the heart called arterial revascularization and chest pain in adults who do not have heart disease but have other multiple risk factors for heart disease.
  - heart attack and stroke in adults with type 2 diabetes mellitus who do not have heart disease but have other multiple risk factors.
  - heart attack that does not cause death, stroke, revascularization, hospitalization for congestive heart failure, and chest pain in adults with heart disease.

It is not known if LIPTRUZET is safe and effective in children.

Do not take LIPTRUZET if you:

- have liver problems (acute liver failure or decompensated cirrhosis)
- are allergic to atorvastatin, ezetimibe, or any of the ingredients in LIPTRUZET. See the end of this leaflet for a complete list of ingredients in LIPTRUZET.

Before taking LIPTRUZET, tell your healthcare provider about all of your medical conditions, including if you:

- have unexplained muscle aches or weakness
- have or have had kidney problems
- have or have had liver problems
- have or have had myasthenia gravis (a disease causing general muscle weakness including in some cases muscles used for breathing), ocular myasthenia (a disease causing eye muscle weakness).
- drink more than 2 glasses of alcohol daily
- have diabetes
- thyroid problems
- had a stroke
- are pregnant, think you may be pregnant, or plan to become pregnant. If you become pregnant while taking LIPTRUZET, call your healthcare provider right away to discuss your LIPTRUZET treatment.
- are breastfeeding. Talk to your healthcare provider about the best way to feed your baby if you take LIPTRUZET. Do not breastfeed while taking LIPTRUZET.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Tell your healthcare provider who prescribes LIPTRUZET if another healthcare provider increases the dose of another medicine you are taking.

LIPTRUZET may affect the way other medicines work, and other medicines may affect how LIPTRUZET works. Especially tell your if you take:

- bile acid sequestrants (medicine for lowering LDL-C)
- rifampin
- birth control pills
- digoxin (medicine for heart failure)
- coumarin anticoagulants (medicines that prevent blood clots, such as warfarin)

Taking LIPTRUZET with certain medicines may increase the risk of muscle problems. Especially tell your healthcare provider if you take:

- cyclosporine (a medicine for your immune system)
- gemfibrozil (a fibric acid medicine for lowering cholesterol)
- anti-viral medicines including certain HIV or hepatitis C drugs such as:
  - tipranavir plus ritonavir
  - lopinavir plus ritonavir
  - saquinavir plus ritonavir
  - fosamprenavir
  - elbasvir plus grazoprevir or letemovir
  - ledipasvir plus sofosbuvir
  - glecaprevir plus pibrentasvir
  - simprevir
  - darunavir plus ritonavir
  - fosamprenavir plus ritonavir
  - nelfinavir
- erythromycin, clarithromycin, itraconazole, ketoconazole, posaconazole, voriconazole
- niacin
- fibrates
- colchicine (medicine for gout)

Also tell your healthcare provider if you drink large amounts of grapefruit juice.
Ask your healthcare provider or pharmacist for a list of medicines if you are not sure. Know all the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take LIPTRUZET?

- Take LIPTRUZET exactly as your healthcare provider tells you to take it.
- Take LIPTRUZET, by mouth, 1 time each day, with or without food.
- **Do not** change your dose or stop LIPTURZET without talking to your healthcare provider, even if you are feeling well.
- Your healthcare provider may do blood tests to check your liver before you start taking LIPTRUZET and during treatment.
- Your health care provider may do blood tests to check your cholesterol levels before and during your treatment with LIPTRUZET. Your health care provider may change your dose of LIPTRUZET if needed.
- While taking LIPTRUZET, continue to follow your cholesterol-lowering diet and to exercise as your healthcare provider told you to.
- If you take a medicine called a bile acid sequestrant, take LIPTRUZET at least 2 hours before or 4 hours after you take the bile acid sequestrant.
- If you take a medicine called rifampin, take LIPTRUZET and rifampin at the same time.
- Tablets should be swallowed whole. Do not crush, dissolve, or chew tablets.
- If you miss a dose, take your next dose at your normal scheduled time. **Do not take** an extra dose of LIPTRUZET.
- In case of an overdose, get medical help or contact a live Poison Center expert right away at 1-800-222-1222. Advice is also available online at poisonhelp.org.

What should I avoid while taking LIPTRUZET?

- Avoid drinking more than 1.2 liters of grapefruit juice each day.
- Avoid drinking more than 2 glasses of alcohol daily.

What are the possible side effects of LIPTRUZET?
LIPTRUZET may cause serious side effects including:

- **Muscle pain, tenderness and weakness (myopathy).** Muscle problems, including muscle breakdown, can be serious in some people and, rarely, cause kidney damage that can lead to death. **Tell your healthcare provider right away if you have:**
  - unexplained muscle pain, tenderness, or weakness, especially if you also have a fever or feel more tired than usual while you take LIPITRUZET.
  - muscle problems that do not go away after your healthcare provider has told you to stop taking LIPITRUZET. Your healthcare provider may do further tests to diagnose the cause of your muscle problems.

  Your chances of getting muscle problems are higher if you:
  - are taking certain other medicines while you take LIPITRUZET (see "Especially tell your healthcare provider if you take")
  - drink large amounts of grapefruit juice
  - are 65 years of age or older
  - have thyroid problems (hypothyroidism) that are not controlled
  - have kidney problems
  - are taking higher doses of LIPITRUZET

- **Liver problems.** Your healthcare provider may do blood tests to check your liver before you start taking LIPITRUZET and if you have symptoms of liver problems while you take LIPITRUZET. Call your healthcare provider right away if you have the following symptoms of liver problems:
  - Feel unusually tired or weak
  - loss of appetite
  - upper belly pain
  - dark urine
  - yellowing of your skin or the whites of your eyes

- **Increase in blood sugar level.** Your blood sugar level may increase while you are taking LIPITRUZET. Exercise regularly and make healthy food choices to maintain healthy body weight.

The most common side effects of LIPTRUZET include:

- changes in your liver function tests
- muscle and body pain
- joint pain
- diarrhea
- tiredness
- upset stomach

Talk to your healthcare provider or pharmacist if you have side effects that bother you or that will not go away.
These are not all the side effects of LIPTRUZET. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LIPTRUZET?

- Store LIPTRUZET at room temperature between 68°F to 77°F (20°C to 25°C).
- **Remove a tablet from the blister only when you are ready to take it.**
- LIPTRUZET is packaged in a cardboard, multi-fold wallet. After you remove a tablet from the folded card, refold the card and slide the card back into the wallet.

Keep LIPTRUZET and all medicines out of the reach of children.

General information about safe and effective use of LIPTRUZET.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LIPTRUZET for a condition for which it was not prescribed. Do not give LIPTRUZET to other people, even if they have the same medical condition you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about LIPTRUZET that is written for health professionals.

What are the ingredients in LIPTRUZET?
Active ingredients: ezetimibe and atorvastatin
Inactive ingredients:
Calcium carbonate, croscarmellose sodium, colloidal silicon dioxide, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, polysorbate, and sodium lauryl sulfate. The tablet film coating contains the following inactive ingredients: hydroxypropyl methylcellulose/hypromellose, macrogol/polyethylene glycol, titanium dioxide, and talc.

This Patient Information has been approved by the U.S. Food and Drug Administration

Organon LLC, a subsidiary of
ORGANON & Co.,
Jersey City, NJ 07302, USA

For patent information: www.organon.com/our solutions/patent/

For more information, go to www.organon.com/our-focus/products-list/ or call 1-844-674-3200.
usppi-og0653c-t-XXXXrXXX

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: X/XXXX