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

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

LIPTRUZET, which contains a cholesterol absorption inhibitor and an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet to:

- reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia. (1.1)
- reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments. (1.2)

Limitations of Use

- No incremental benefit of LIPTRUZET on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has been established. LIPTRUZET has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias. (1.3)

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

- Dosage range is 10/10 mg/day through 10/80 mg/day. (2.1)
- Recommended starting dose is 10/10 mg/day or 10/20 mg/day. (2.1)
- Recommended starting dose is 10/40 mg/day for patients requiring a >55% reduction in LDL-C. (2.1)
- Dosing of LIPTRUZET should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant. (2.3, 7.11)

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

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

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

- Active liver disease or unexplained persistent elevations of hepatic transaminase levels. (4, 5.2)
- Hypersensitivity to any component of LIPTRUZET. (4, 6.2)
- Women who are pregnant or may become pregnant. (4, 8.1)
- Nursing mothers. (4, 8.3)

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

- Patients should be advised to report promptly any unexplained and/or persistent muscle pain, tenderness, or weakness. LIPTRUZET should be discontinued immediately if myopathy is diagnosed or suspected. (5.1)
- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain CYP3A4 inhibitors, fibric acid derivatives, and cyclosporine. Predisposing factors include advanced age (>65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. (5.1, 8.5)
- Liver enzyme abnormalities: Persistent elevations in hepatic transaminase can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter. (5.2)

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

- 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 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis with Atorvastatin (2.3, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations for LIPTRUZET
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir), gemfibrozil	Avoid LIPTRUZET
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary.
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 10/20 mg LIPTRUZET daily.
HIV protease inhibitor (nelfinavir), hepatitis C protease inhibitor (boceprevir)	Do not exceed 10/40 mg LIPTRUZET daily.

- Other lipid-lowering medications: Use with fenofibrates or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with LIPTRUZET. (7)
- Fenofibrates: Combination increases exposure of ezetimibe. If cholelithiasis is suspected in a patient receiving ezetimibe and a fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered. (7.5, 12.3)
- Cholestyramine: Combination decreases exposure of ezetimibe. (2.3, 12.3)
- Digoxin: Patients should be monitored appropriately. (7.7)
- Oral contraceptives: Values for norethindrone and ethinyl estradiol may be increased. (7.8)
- Rifampin should be simultaneously coadministered with LIPTRUZET. (7.9)

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

- Hepatic impairment: Plasma concentrations of atorvastatin are markedly increased in patients with chronic alcoholic liver disease. (8.6, 12.3)

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

Revised: 05/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate.

1.1 Primary Hyperlipidemia

LIPTRUZET™ is indicated for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia.

1.2 Homozygous Familial Hypercholesterolemia (HoFH)

LIPTRUZET is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

1.3 Limitations of Use

No incremental benefit of LIPTRUZET on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has been established. LIPTRUZET has not been studied in Fredrickson type I, III, IV, and V dyslipidemias.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosage range of LIPTRUZET is 10/10 mg/day to 10/80 mg/day. The recommended starting dose of LIPTRUZET is 10/10 mg/day or 10/20 mg/day. LIPTRUZET can be administered as a single dose at any time of the day, with or without food. The recommended starting dose for patients who require a larger reduction in LDL-C (greater than 55%) is 10/40 mg/day. After initiation and/or upon titration of LIPTRUZET, lipid levels should be analyzed within 2 or more weeks and dosage adjusted accordingly.

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

2.2 Patients with Homozygous Familial Hypercholesterolemia

The dosage of LIPTRUZET in patients with homozygous familial hypercholesterolemia is 10/40 mg/day or 10/80 mg/day. 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.

2.3 Coadministration with Other Drugs

Bile Acid Sequestrants

Dosing of LIPTRUZET should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant *[see Drug Interactions (7.11)]*.

Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with LIPTRUZET should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing LIPTRUZET and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a

combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with LIPTRUZET should be limited to 10/20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPTRUZET is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with LIPTRUZET should be limited to 10/40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of LIPTRUZET is employed. *[See Warnings and Precautions (5.1) and Drug Interactions (7).]*

Other Concomitant Lipid-Lowering Therapy

The combination of LIPTRUZET and gemfibrozil is not recommended *[see Warnings and Precautions (5.1) and Drug Interactions (7.4)]*.

3 DOSAGE FORMS AND STRENGTHS

- LIPTRUZET™ 10 mg/10 mg (ezetimibe 10 mg/atorvastatin 10 mg) tablets are white to off-white capsule-shaped, biconvex film-coated tablets with code “320” on one side.
- LIPTRUZET™ 10 mg/20 mg (ezetimibe 10 mg/atorvastatin 20 mg) tablets are white to off-white round, biconvex film-coated tablets with code “321” on one side.
- LIPTRUZET™ 10 mg/40 mg (ezetimibe 10 mg/atorvastatin 40 mg) tablets are white to off-white oval, biconvex film-coated tablets with code “322” on one side.
- LIPTRUZET™ 10 mg/80 mg (ezetimibe 10 mg/atorvastatin 80 mg) tablets are white to off-white capsule-shaped, biconvex film-coated tablets with code “323” on one side.

4 CONTRAINDICATIONS

Active liver disease or unexplained persistent elevations of hepatic transaminase levels.

Hypersensitivity to any component of LIPTRUZET *[see Adverse Reactions (6.2)]*.

Women who are pregnant or may become pregnant. LIPTRUZET may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of LIPTRUZET use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. LIPTRUZET should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, LIPTRUZET should be discontinued immediately, and the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

Nursing mothers. It is not known whether atorvastatin is excreted into human milk; however, a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require LIPTRUZET treatment should not breast-feed their infants *[see Use in Specific Populations (8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

Atorvastatin

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

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times upper limit of normal (ULN). The concomitant use of higher doses of atorvastatin with certain drugs such as

cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatinine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing LIPTRUZET. LIPTRUZET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with statins is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with LIPTRUZET and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of LIPTRUZET should be considered when taken concomitantly with the aforementioned drugs. *[See Drug Interactions (7).]* Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 1 *[*see also *Dosage and Administration (2.3), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Table 1: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis with Atorvastatin

Interacting Agents	Prescribing Recommendations for LIPTRUZET
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir), gemfibrozil	Avoid LIPTRUZET.
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary.
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 10/20 mg LIPTRUZET daily.
HIV protease inhibitor (nelfinavir), hepatitis C protease inhibitor (boceprevir)	Do not exceed 10/40 mg LIPTRUZET daily.

*Use with caution and with the lowest dose necessary *[see Clinical Pharmacology (12.3)]*

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin coadministered with colchicine, and caution should be exercised when prescribing LIPTRUZET with colchicine *[*see *Drug Interactions (7.10)]*.

LIPTRUZET therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Ezetimibe

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone). However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. In clinical trials, the incidence of creatine phosphokinase (CPK) >10 times ULN was 0.2% for ezetimibe vs. 0.1% for placebo, and 0.1% for ezetimibe coadministered with a statin vs. 0.4% for statins alone. Risk for skeletal muscle toxicity increases with higher doses of statin, advanced age (>65), hypothyroidism, renal impairment, and depending on the statin used, concomitant use of other drugs.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported with ezetimibe monotherapy and with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibric acid derivatives. LIPTRUZET and a fenofibrate, if taking concomitantly, should both be immediately discontinued if myopathy is diagnosed or suspected. The presence of muscle symptoms and a CPK level >10 times the ULN indicates myopathy.

5.2 Liver Enzymes

Atorvastatin

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times ULN occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg atorvastatin, respectively.

One patient in clinical trials of atorvastatin developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

Ezetimibe

In controlled clinical studies, the incidence of consecutive elevations (≥3 times ULN) in hepatic transaminase levels was similar between ezetimibe (0.5%) and placebo (0.3%).

In controlled clinical combination studies of ezetimibe coadministered with atorvastatin, the incidence of consecutive elevations (≥3 times ULN) in hepatic transaminase levels was 0.6% for patients treated with ezetimibe administered with atorvastatin. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.

LIPTRUZET

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

LIPTRUZET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of LIPTRUZET *[see Contraindications (4)]*.

5.3 Endocrine Function

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

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

5.4 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin 80 mg vs. placebo was administered in 4,731 subjects without CHD

who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin 80 mg group compared to placebo (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.

5.5 CNS Toxicity

Atorvastatin

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human $AUC_{(0-24)}$ based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

6 ADVERSE REACTIONS

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

- Rhabdomyolysis and myopathy *[see Warnings and Precautions (5.1)]*
- Liver enzyme abnormalities *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

LIPTRUZET

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

In a LIPTRUZET (ezetimibe and atorvastatin) placebo-controlled clinical trial, 628 patients (age range 18-86 years, 59% women, 85% Caucasians, 6% Blacks, 5% Hispanics, 3% Asians) with a median treatment duration of 12 weeks, 6% of patients on LIPTRUZET and 5% of patients on placebo discontinued due to adverse reactions.

The most common adverse reactions in the group treated with LIPTRUZET 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%).

LIPTRUZET has been evaluated for safety in 2403 patients in 7 clinical trials (one placebo-controlled trial and six active-controlled trials).

Table 2 summarizes the frequency of clinical adverse reactions reported in ≥2% of patients treated with LIPTRUZET (n=255) and at an incidence greater than placebo, regardless of causality assessment, from the placebo-controlled trial.

Table 2*: Clinical and Selected Laboratory Adverse Reactions Occurring in ≥2% of Patients Treated with LIPTRUZET and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Reaction	Placebo (%) n=60	Ezetimibe 10 mg (%) n=65	Atorvastatin† (%) n=248	LIPTRUZET† (%) n=255
Nervous system disorders				
Dizziness	0	6	<1	2
Respiratory, thoracic, and mediastinal disorders				
Coughing	0	3	<1	2
Gastrointestinal disorders				
Abdominal pain	2	2	4	3
Nausea	0	2	5	3
Musculoskeletal and connective tissue disorders				
Arthralgia	0	5	6	3
Muscle weakness	0	2	0	2
Musculoskeletal pain	3	8	5	4
Metabolism and nutrition disorders				
Hyperkalemia	0	0	<1	2
Infections and infestations				
Bronchitis	0	2	2	2
Sinusitis	0	3	2	2
Vascular disorders				
Hot flushes	0	0	<1	2
Investigations				
ALT increased	0	0	2	5
AST increased	0	0	<1	4

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

After completing the 12-week study, eligible patients were assigned to coadministered ezetimibe and atorvastatin equivalent to LIPTRUZET (10/10-10/80) 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, 2396 patients with primary hyperlipidemia (age range 9-86 years, 50% women, 90% Caucasians, 5% Blacks, 3% Hispanics, 2% Asians) 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 regardless of causality assessment are shown in Table 3.

Table 3: Clinical Adverse Reactions Occurring in ≥2% of Patients Treated with Ezetimibe and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Reaction	Ezetimibe 10 mg (%) n=2396	Placebo (%) n=1159
Gastrointestinal disorders		
Diarrhea	4.1	3.7
General disorders and administration site conditions		
Fatigue	2.4	1.5
Infections and infestations		
Influenza	2.0	1.5
Sinusitis	2.8	2.2
Upper respiratory tract infection	4.3	2.5
Musculoskeletal and connective tissue disorders		
Arthralgia	3.0	2.2
Pain in extremity	2.7	2.5

Atorvastatin

In an atorvastatin placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin vs. 7311 placebo; age range 10–93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality.

The most commonly reported adverse reactions (incidence ≥2% and greater than placebo) regardless of causality, in patients treated with atorvastatin in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

Table 4 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥2% and at a rate greater than placebo in patients treated with atorvastatin (n=8755), from seventeen placebo-controlled trials.

Table 4: Clinical Adverse Reactions Occurring in > 2% in Patents Treated with any dose of Atorvastatin and at an Incidence Greater than Placebo Regardless of Causality (% of patients).

Adverse Reaction*	Any dose n=8755	Atorvastatin 10 mg n=3908	Atorvastatin 20 mg n=188	Atorvastatin 40 mg n=604	Atorvastatin 80 mg n=4055	Placebo n=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1

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

6.2 Postmarketing Experience

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.

The additional events described below have been identified during post-approval use of ezetimibe and/or atorvastatin.

Blood and lymphatic system disorders: thrombocytopenia

Nervous system disorders: headache; paresthesia; peripheral neuropathy

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

Gastrointestinal disorders: pancreatitis

Skin and subcutaneous tissue disorders: angioedema; bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis); rash; urticaria

Musculoskeletal and connective tissue disorders: myopathy/rhabdomyolysis *[see Warnings and Precautions (5.1)]*

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use *[see Warnings and Precautions (5.1)]*.

Injury, poisoning and procedural complications: tendon rupture

Immune system disorders: anaphylaxis; hypersensitivity reactions

Hepatobiliary disorders: hepatitis; cholelithiasis; cholecystitis; fatal and nonfatal hepatic failure

Psychiatric disorders: depression

Laboratory abnormalities: elevated creatine phosphokinase

7 DRUG INTERACTIONS

[See Clinical Pharmacology (12.3).]

LIPTRUZET

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) *[see Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)]*.

7.1 Strong Inhibitors of Cytochrome P450 3A4

Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin with strong inhibitors of CYP3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP3A4. Because LIPTRUZET contains atorvastatin, the risk of myopathy during treatment with LIPTRUZET is increased with concurrent administration of:

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of 80 mg atorvastatin with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking clarithromycin, caution should be used when the LIPTRUZET dose exceeds 10/20 mg *[see Warnings and Precautions (5.1) and Dosage and Administration (2.3)]*.

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of LIPTRUZET should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing LIPTRUZET and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of LIPTRUZET should not exceed 10/20 mg and should be used with caution *[see Warnings and Precautions (5.1)* and *Dosage and Administration (2.3)]*. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of LIPTRUZET should not exceed 10/40 mg daily and close clinical monitoring is recommended.

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking itraconazole, do not use a LIPTRUZET dose that exceeds 10/20 mg *[see Warnings and Precautions (5.1)* and *Dosage and Administration (2.3)]*.

7.2 Cyclosporine

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin alone *[see Clinical Pharmacology (12.3)]*.

In addition, ezetimibe and cyclosporine used concomitantly can increase exposure to both ezetimibe and cyclosporine. The degree of increase in ezetimibe exposure may be greater in patients with severe renal impairment.

The coadministration of LIPTRUZET with cyclosporine should be avoided *[see Warnings and Precautions (5.1)]*.

7.3 Grapefruit Juice

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

7.4 Gemfibrozil

Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are coadministered with gemfibrozil, concomitant administration of LIPTRUZET with gemfibrozil should be avoided *[see Warnings and Precautions (5.1)]*.

7.5 Fenofibrates (e.g., fenofibrate and fenofibric acid)

Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of fenofibrates, LIPTRUZET should be administered with caution when used concomitantly with a fenofibrate *[see Warnings and Precautions (5.1)]*.

Fenofibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected in a patient receiving LIPTRUZET and a fenofibrate, gallbladder studies are indicated and

alternative lipid-lowering therapy should be considered *[see the product labeling for fenofibrate and fenofibric acid]*.

7.6 Niacin

The risk of skeletal muscle effects may be enhanced when LIPTRUZET is used in combination with niacin; a reduction in LIPTRUZET dosage should be considered in this setting *[see Warnings and Precautions (5.1)]*.

7.7 Digoxin

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

7.8 Oral Contraceptives

Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol *[see Clinical Pharmacology (12.3)]*. These increases should be considered when selecting an oral contraceptive for a woman taking LIPTRUZET.

7.9 Rifampin or Other Inducers of Cytochrome P450 3A4

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous coadministration of LIPTRUZET with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.10 Colchicine

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

7.11 Cholestyramine

Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be reduced by this interaction.

7.12 Coumarin Anticoagulants

If LIPTRUZET is added to warfarin, a coumarin anticoagulant, the International Normalized Ratio (INR) should be appropriately monitored.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X.

[See Contraindications (4).]

LIPTRUZET

LIPTRUZET is contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy. Lipid-lowering drugs offer no benefit during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.

There are no adequate and well-controlled studies of LIPTRUZET use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Statins may cause fetal harm when administered to a pregnant woman. Because LIPTRUZET contains atorvastatin, LIPTRUZET should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking LIPTRUZET, it should be discontinued immediately and the patient advised again as to the potential hazards to the fetus and the lack of known clinical benefit with continued use during pregnancy.

Ezetimibe

In oral (gavage) embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis, there was no evidence of embryolethal effects at the doses tested (250, 500, 1000 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 1000 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 1000 mg/kg/day (150 times the human exposure at 10 mg daily based on $AUC_{0\text{-}24hr}$ for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.

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

Atorvastatin

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2).

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation Day 7 through to lactation Day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on Days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at Days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod 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 AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to statin reductase inhibitors.

8.3 Nursing Mothers

In rat studies, exposure to total ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe is excreted into human breast milk.

It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Nursing rat pups had plasma and liver atorvastatin levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking LIPTRUZET should not breast-feed *[see Contraindications (4)]*.

8.4 Pediatric Use

LIPTRUZET

Safety and effectiveness have not been established in pediatric patients.

Ezetimibe

Based on total ezetimibe (ezetimibe + ezetimibe-glucuronide) there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the pediatric population <10 years of age are not available.

Atorvastatin

Pharmacokinetic data in the pediatric population are not available.

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 Hepatic Impairment

LIPTRUZET is contraindicated in patients with active liver disease or unexplained persistent elevations in hepatic transaminase levels *[see Contraindications (4), Warnings and Precautions (5.2), and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

A history of renal impairment may be a risk factor for statin-associated 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.

10 OVERDOSAGE

LIPTRUZET

No specific treatment of overdosage with LIPTRUZET can be recommended. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

Ezetimibe

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hyperlipidemia for up to 56 days, and 40 mg/day to 27 patients with homozygous sitosterolemia for 26 weeks, was generally well tolerated. One female patient with homozygous sitosterolemia took an accidental overdose of ezetimibe 120 mg/day for 28 days with no reported clinical or laboratory adverse events.

Atorvastatin

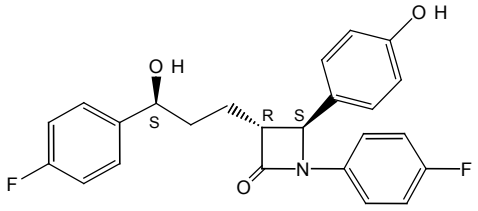
Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

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.

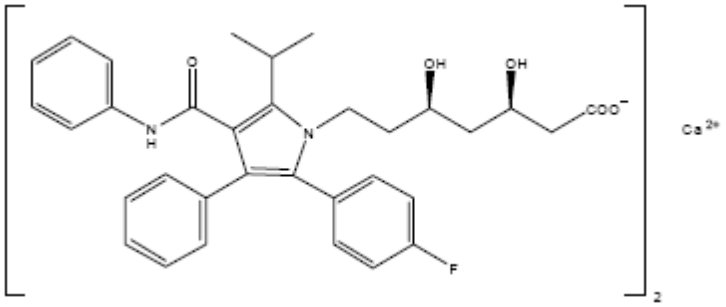
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4.

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).

Atorvastatin calcium is a white to off-white amorphous powder that is very slightly soluble in water, insoluble in acetonitrile, and soluble in methanol. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca$. The molecular weight of atorvastatin calcium is 1155.37. Its structural formula is:



LIPTRUZET is available for oral use as tablets containing 10 mg of ezetimibe and: 10.34 mg of atorvastatin calcium, equivalent to 10 mg of atorvastatin (LIPTRUZET 10 mg/10 mg); 20.68 mg of atorvastatin calcium, equivalent to 20 mg of atorvastatin (LIPTRUZET 10 mg/20 mg); 41.37 mg of atorvastatin calcium, equivalent to 40 mg of atorvastatin (LIPTRUZET 10 mg/40 mg); or 82.73 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: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, lactose anhydrous, hydroxypropyl cellulose, and sodium bicarbonate. In addition, the film coating contains the following inactive ingredients: hydroxypropyl cellulose, hypromellose, titanium dioxide, and carnauba wax.

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 with complementary mechanisms of action.

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. 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.

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 clearance of cholesterol from the blood; this distinct mechanism is complementary to that of statins *[see Clinical Studies (14)]*.

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

Clinical studies have demonstrated that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote

atherosclerosis. The independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

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

LIPTRUZET

LIPTRUZET 10/10 and 10/80 tablets have been shown to be bioequivalent to coadministration of corresponding doses of ezetimibe and atorvastatin tablets. LIPTRUZET 10/20 and 10/40 tablets have been shown to be clinically equivalent in LDL-C response to the corresponding coadministered doses of ezetimibe and atorvastatin tablets. *[See Clinical Studies (14.1).]*

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 on Oral Absorption

LIPTRUZET

A high-fat meal decreased atorvastatin AUC and C_{max} 11% and 35%, respectively, of the LIPTRUZET 10/80 tablet. A high-fat meal decreased unconjugated ezetimibe AUC 2% and increased unconjugated ezetimibe C_{max} 10% of the LIPTRUZET 10/80 tablet.

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. Based on observations in rats, atorvastatin is likely to be secreted in human milk *[see Contraindications (4); Use in Specific Populations (8.3)]*.

Metabolism and Excretion

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.

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 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.

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. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults.

Pediatric Patients*: [See Use in Specific Populations (8.4).]*

Gender

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 women than in men.

Atorvastatin

Plasma concentrations of atorvastatin in women differ from those in men (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 men and women.

Race

Ezetimibe

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

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)]*.

Renal Impairment

[See Warnings and Precautions (5.1), Use in Specific Populations (8.7)]

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.

Hemodialysis

Atorvastatin

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

Drug Interactions [See also Drug Interactions (7).]

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

Cytochrome P450: 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.

Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of LIPTRUZET with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of the atorvastatin component of LIPTRUZET. The extent of interaction and potentiation of effects depends on the variability of effect on cytochrome P450 3A4.

Ezetimibe

Table 5: 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 6: 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

Table 7: Effect of Coadministered Drugs on the Pharmacokinetics of Atorvastatin

Coadministered Drug and Dosing Regimen	Atorvastatin

	Dose (mg)	Change in AUC*	Change in C_{max}*
Cyclosporine 5.2 mg/kg/day, stable dose†	10 mg QD for 28 days	↑8.7 fold	↑10.7 fold
Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days†	10 mg, SD	↑9.4 fold	↑8.6 fold
Telaprevir 750 mg q8h, 10 days†	20 mg, SD	↑7.88 fold	↑10.6 fold
Saquinavir 400 mg BID/ritonavir 400 mg BID, 15 days†,#	40 mg QD for 4 days	↑3.9 fold	↑4.3 fold
Clarithromycin 500 mg BID, 9 days†	80 mg QD for 8 days	↑4.4 fold	↑5.4 fold
Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days†	10 mg QD for 4 days	↑3.4 fold	↑2.25 fold
Itraconazole 200 mg QD, 4 days†	40 mg, SD	↑3.3 fold	↑20%
Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days†	10 mg QD for 4 days	↑2.53 fold	↑2.84 fold
Fosamprenavir 1400 mg BID, 14 days†	10 mg QD for 4 days	↑2.3 fold	↑4.04 fold
Nelfinavir 1250 mg BID, 14 days†	10 mg QD for 28 days	↑74%	↑2.2 fold
Grapefruit Juice, 240 mL QD†,‡	40 mg, SD	↑37%	↑16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑51%	No change
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑33%	↑38%
Amlodipine 10 mg, single dose	80 mg, SD	↑15%	↓12%
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓Less than 1%	↓11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓26%§
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓33%	↓34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓41%	↓1%
Rifampin 600 mg QD, 7 days (coadministered) †,¶	40 mg, SD	↑30%	↑2.7 fold
Rifampin 600 mg QD, 5 days (doses separated) †,¶	40 mg, SD	↓80%	↓40%
Gemfibrozil 600 mg BID, 7 days†	40 mg, SD	↑35%	↓Less than 1%
Fenofibrate 160 mg QD, 7 days†	40 mg, SD	↑3%	↑2%
Boceprevir 800 mg TID, 7 days	40 mg, SD	↑2.30 fold	↑2.66 fold

* Data given as x-fold change represent a simple ratio between coadministration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

† *See Warnings and Precautions (5.1)* and *Drug Interactions (7)* for clinical significance.

‡ Greater increases in AUC (up to 2.5 fold) and/or C_{max} (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).

§ Single sample taken 8-16 h post-dose.

¶ Due to the dual interaction mechanism of rifampin, simultaneous coadministration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

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.

Table 8: 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 for 15 days	Antipyrine, 600 mg SD	↑3%	↓11%
80 mg QD for 14 days	Digoxin 0.25 mg QD, 20 days*	↑15%	↑20%
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1 mg - ethinyl estradiol 35 µg	↑28% ↑19%	↑23% ↑30%
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓27%	↓18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

* *See Drug Interactions (7)* for clinical significance.

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.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with

100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80-mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

13.2 Animal Toxicology and/or Pharmacology

Ezetimibe

In a rat model, where the glucuronide metabolite of ezetimibe (ezetimibe-glucuronide) was administered intraduodenally, the metabolite was as potent as ezetimibe in inhibiting the absorption of cholesterol, suggesting that the glucuronide metabolite had activity similar to the parent drug.

In 1-month studies in dogs given ezetimibe (0.03 to 300 mg/kg/day), the concentration of cholesterol in gallbladder bile increased ~2- to 4-fold. However, a dose of 300 mg/kg/day administered to dogs for one year did not result in gallstone formation or any other adverse hepatobiliary effects. In a 14-day study in mice given ezetimibe (0.3 to 5 mg/kg/day) and fed a low-fat or cholesterol-rich diet, the concentration of cholesterol in gallbladder bile was either unaffected or reduced to normal levels, respectively.

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

In 4- to 12-week toxicity studies in mice, ezetimibe did not induce cytochrome P450 drug metabolizing enzymes. In toxicity studies, a pharmacokinetic interaction of ezetimibe with statins (parents or their active hydroxy acid metabolites) was seen in rats, dogs, and rabbits.

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

LIPTRUZET – Lipid Efficacy

LIPTRUZET reduces total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C in patients with hypercholesterolemia.

LIPTRUZET is effective in men and women with hyperlipidemia. Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of LIPTRUZET.

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

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

Patients receiving all doses of LIPTRUZET were compared to those receiving all doses of atorvastatin. LIPTRUZET lowered total-C, LDL-C, Apo B, TG, and non-HDL-C, and increased HDL-C significantly more than atorvastatin alone. (See Table 9.)

Table 9: Response to LIPTRUZET 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 LIPTRUZET 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]
LIPTRUZET by dose							
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 by dose							
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
‡ LIPTRUZET pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, non-HDL-C, and significantly increased HDL-C compared to all doses of atorvastatin pooled (10-80 mg).
§ 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 LIPTRUZET (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 study) who agreed to participate in the study extension.

A multicenter, double-blind, controlled, 14-week study was conducted in 621 patients with heterozygous familial hypercholesterolemia (HeFH), coronary heart disease (CHD), or multiple cardiovascular risk factors (≥2), adhering to an NCEP Step I or stricter diet. All patients received atorvastatin 10 mg for a minimum of 4 weeks prior to randomization. Patients were then randomized to receive either coadministered ezetimibe and atorvastatin (equivalent to LIPTRUZET 10/10) or atorvastatin 20 mg/day monotherapy. Patients who did not achieve their LDL-C target goal after 4 and/or 9 weeks of randomized treatment were titrated to double the atorvastatin dose.

The patient population was: 47% female; 91% Caucasian, 2% Black, 2% Asian, 5% Hispanic, <1% other; 18 to 82 years of age (mean age 61 years).

LIPTRUZET 10/10 was significantly more effective than doubling the dose of atorvastatin to 20 mg in further reducing total-C, LDL-C, TG, and non-HDL-C. Results for HDL-C between the two treatment groups were not significantly different. (See Table 10.) In addition, at Week 4 significantly more patients receiving LIPTRUZET 10/10 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 LIPTRUZET 10/10 and atorvastatin 20 mg were 186 mg/dL and 187 mg/dL, respectively.

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

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

LIPTRUZET 10/20 was significantly more effective than doubling the dose of atorvastatin to 40 mg in further reducing total-C, LDL-C**,** Apo B and non-HDL-C. Results for HDL-C and TG between the two treatment groups were not significantly different. (See Table 11.) In addition, significantly more patients receiving LIPTRUZET 10/20 attained LDL-C <100 mg/dL (<2.6 mmol/L) compared to those receiving atorvastatin 40 mg, 84% vs. 49%.

Table 11: Response to LIPTRUZET 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‡]
LIPTRUZET 10/20	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 LIPTRUZET 10/20 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) study, a multicenter, double-blind, controlled, 6-week study, included 556 patients with an LDL-C level ≥70 mg/dL and ≤160 mg/dL (≥1.8 mmol/L and ≤4.1 mmol/L) 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 (<1.8 mmol/L) were randomized to receive either coadministered ezetimibe and atorvastatin (equivalent to LIPTRUZET 10/40) or atorvastatin 80 mg for 6 weeks.

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

LIPTRUZET 10/40 was significantly more effective than doubling the dose of atorvastatin to 80 mg in further reducing total-C, LDL-C**,** Apo B, TG, and non-HDL-C. Results for HDL-C between the two treatment groups were not significantly different. (See Table 12.) In addition, significantly more patients receiving LIPTRUZET 10/40 attained LDL-C <70 mg/dL (<1.8 mmol/L) compared to those receiving atorvastatin 80 mg, 74% vs. 32%.

Table 12: Response to LIPTRUZET 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‡]
LIPTRUZET 10/40	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 LIPTRUZET 10/40 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

LIPTRUZET 10/20 and 10/40 - Clinical Equivalence to Coadministered Components

LIPTRUZET has been shown to be bioequivalent to coadministration of corresponding doses of its ezetimibe and atorvastatin components with the exception of slightly lower atorvastatin C_{max} for the 10/20 and 10/40 mg doses *[see Clinical Pharmacology (12.3)]*, which, in two separate studies, have been shown to be clinically equivalent in LDL-C response after six weeks of treatment to their corresponding coadministered components.

In these two multicenter, double-blind, controlled, crossover studies, patients with primary hypercholesterolemia and low, moderate, or moderately high cardiovascular risk received LIPTRUZET 10/20-mg (Study 1) or 10/40-mg (Study 2) tablets or the corresponding coadministered components once daily for 6 weeks. They then crossed over, after a 6-week washout, to the coadministered components or LIPTRUZET at corresponding doses for an additional 6 weeks. From untreated baseline, mean changes in LDL-C for LIPTRUZET vs. the coadministered components, respectively, were -54.0% vs. -53.8% for 10/20-mg (Study 1), and -58.9% vs. -58.7% for 10/40-mg (Study 2). Mean changes for total-C, Apo B, TG, non-HDL-C, and HDL-C were also similar between the two treatment groups and supported the conclusion of clinical equivalence.

14.2 Homozygous Familial Hypercholesterolemia (HoFH)

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

After completing the 12-week study, eligible patients (n=35), who were receiving atorvastatin 40 mg at baseline, were assigned to coadministered ezetimibe and atorvastatin equivalent to LIPTRUZET 10/40 for up to an additional 24 months. Following at least 4 weeks of treatment, the atorvastatin dose could be doubled to a maximum dose of 80 mg.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets LIPTRUZET 10 mg/10 mg are white to off-white capsule-shaped, biconvex film-coated tablets with code “320” on one side.

They are supplied as follows:

NDC 66582-320-30 unit of use packages of 30 (three foil pouches each containing one 10-count blister card)

NDC 66582-320-54 unit of use packages of 90 (nine foil pouches each containing one 10-count blister card)

Tablets LIPTRUZET 10 mg/20 mg are white to off-white round, biconvex film-coated tablets with code “321” on one side.

They are supplied as follows:

NDC 66582-321-30 unit of use packages of 30 (three foil pouches each containing one 10-count blister card)

NDC 66582-321-54 unit of use packages of 90 (nine foil pouches each containing one 10-count blister card)

Tablets LIPTRUZET 10 mg/40 mg are white to off-white oval, biconvex film-coated tablets with code “322” on one side.

They are supplied as follows:

NDC 66582-322-30 unit of use packages of 30 (three foil pouches each containing one 10-count blister card)

NDC 66582-322-54 unit of use packages of 90 (nine foil pouches each containing one 10-count blister card)

Tablets LIPTRUZET 10 mg/80 mg are white to off-white capsule-shaped, biconvex film-coated tablets with code “323” on one side.

They are supplied as follows:

NDC 66582-323-30 unit of use packages of 30 (three foil pouches each containing one 10-count blister card)

NDC 66582-323-54 unit of use packages of 90 (nine foil pouches each containing one 10-count blister card)

Storage of Unit of Use Packages of 30 and 90

Store LIPTRUZET at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in the foil pouch until use. After the foil pouch is opened, protect LIPTRUZET from moisture and light. Once a tablet is removed, slide blister card back into case. Store the case in a dry place, and discard any unused tablets 30 days after the pouch is opened.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

17.1 Muscle Pain

All patients starting therapy with LIPTRUZET should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing LIPTRUZET. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (>1 liter) of grapefruit juice. Patients should discuss all medication, both prescription and over-the-counter, with their physician.

17.2 Liver Enzymes

It is recommended that liver enzyme tests be performed before the initiation of LIPTRUZET and if signs or symptoms of liver injury occur. All patients treated with LIPTRUZET should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using LIPTRUZET. Discuss future pregnancy plans with your patients, and discuss when to stop taking LIPTRUZET if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking LIPTRUZET and call their healthcare professional.

17.4 Breast-Feeding

Women who are breast-feeding should be advised to not use LIPTRUZET. Patients who have a lipid disorder and are breast-feeding should be advised to discuss the options with their healthcare professionals.

17.5 Important Storage and Administration Instructions

Patients should be advised to store LIPTRUZET at room temperature, 20-25°C (68-77°F). They should also be advised:

- not to open a pouch until they are ready to use LIPTRUZET
- that after the foil pouch is opened, LIPTRUZET should be protected from moisture and light, and stored in a dry place
- that for packages containing a plastic case (unit of use packages of 30 and 90), once they remove a tablet from the blister card, they should slide the blister card back into the plastic case
- to discard any unused tablets 30 days after the pouch is opened

Tablets should be swallowed whole. Do not crush, dissolve, or chew tablets.

If a dose is missed, the patient should not take an extra dose. Just resume the usual schedule.

Manufactured by:

Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

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