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

ROSZET (rosuvastatin and ezetimibe) tablets, for oral use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.2), (5.3) 08/24

----------INDICATIONS AND USAGE----------
ROSZET is a combination of rosuvastatin, an HMG CoA-reductase inhibitor (statin), and ezetimibe, a dietary cholesterol absorption inhibitor, indicated:
- As an adjunct to diet in adults with primary non-familial hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C). (1)
- Alone or as an adjuct to other LDL-C lowering therapies in adults with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C. (1)

----------DOSAGE AND ADMINISTRATION----------
- Swallow tablets whole; do not crush, dissolve or chew. (2.1)
- Dosage range is 5 mg/10 mg to 40 mg/10 mg once daily. (2.1)
- Recommended dosage depends on the indication for usage, LDL-C, and individual risk for cardiovascular events. (2.1)
- Assess LDL-C as early as 2 weeks after initiating ROSZET, and adjust dosage as necessary. (2.1)
- *Asian patients*: Initiate at 5 mg/10 mg once daily. (2.2)
- *Patients with severe renal impairment (not on hemodialysis):* initiate at 5 mg/10mg once daily; do not exceed 10 mg/10 mg once daily. (2.3)
- See full prescribing information for ROSZET dosage and administration modifications due to drug interactions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets (rosuvastatin/ezetimibe): 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg. (3)

----------CONTRAINDICATIONS----------
- Acute liver failure or decompensated cirrhosis (4)
- Hypersensitivity to rosuvastatin, ezetimibe, or any excipitents in ROSZET (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 ROSZET dosage. Asian patients may be at higher risk for myopathy. Discontinue ROSZET if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Temporarily discontinue ROSZET 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 ROSZET 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 ROSZET 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 enzyme before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue ROSZET. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions for:
- Rosuvastatin (incidence ≥2% and greater than placebo) are headache, nausea, myalgia, asthenia, and constipation. (6.1)
- Ezetimibe (incidence ≥2% and greater than placebo) are upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity, and fatigue. (6.1)
- Ezetimibe co-administered with a statin (incidence ≥2% and greater than statin alone) are nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea, back pain, influenza, and pain in extremity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Althera Pharmaceuticals LLC at 1-877-495-3908 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
See full prescribing information for details regarding concomitant use of ROSZET with othe drugs that increase the risk of of myopathy and rhabdomyolysis (7.1)
- *Gemfibrozil or Cyclosporin*: Avoid concomitant use with ROSZET. (7.1)
- *Fenofibrates, Niacin, Colchine*: Consider the risks and benefits of concomitant use with ROSZET. (7.1)
- *Bile Acid Sequestrants:* Cholestyramine combination decreases exposure of ROSZET (7.2)
- Aluminum and Magnesium Hydroxide Combination Antacids: Administer ROSZET at least 2 hours before the antacid (7.2).
- *Warfarin*: Obtain INR before ROSZET initiation. Monitor INR frequently until stable upon initiation, dose titration, or discontinuation(7.3)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy:* May cause fetal harm. (8.1)
- *Lactation:* Breastfeeding not recommended during treatment with ROSZET. (8.2)

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

Revised: 08/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ROSZET is indicated in adults:

- As an adjunct to diet in patients with primary non-familial hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).
- Alone or as an adjunct to other LDL-C-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration Information

- Swallow ROSZET tablets whole at any time of the day, with or without food. Do not crush, dissolve, or chew tablets.
- The recommended dosage range of ROSZET is one tablet (containing 5 mg to 40 mg of rosuvastatin and 10 mg of ezetimibe) orally once daily.
- The recommended dose of ROSZET depends on a patient's indication for usage, LDL-C, and individual risk for cardiovascular events.
- The starting dosage for patients switching to ROSZET from co-administration of a statin and ezetimibe is based on an equivalent dose of rosuvastatin and 10 mg of ezetimibe.
- Assess LDL-C when clinically appropriate, as early as 2 weeks after initiating ROSZET, and adjust the dosage if necessary.
- If a dose is missed, advise patients not take an extra dose. Resume treatment with the next dose.
- In patients taking a bile acid sequestrant, administer ROSZET at least 2 hours before or 4 hours after the bile acid sequestrant *[see Drug Interactions (7.2)].*
- When taking ROSZET with an aluminum and magnesium hydroxide combination antacid, administer ROSZET at least 2 hours before the antacid *[see Drug Interactions (7.2)]*.

2.2 Recommended Dosage in Asian Patients

Initiate ROSZET at 5 mg/10 mg daily due to increased rosuvastatin plasma concentrations. Consider the risk/benefit when treating Asian patients not adequately controlled at doses up to 20 mg/10 mg once daily *[see Warnings and Precautions (5.1), Use in Specific Populations (8.8), and Clinical Pharmacology (12.3)].*

2.3 Recommended Dosage in Patients with Renal Impairment

In patients with severe renal impairment (CL_{cr} less than 30 mL/min/1.73 m^2) not on hemodialysis, the recommended starting dosage is 5 mg/10 mg once daily and should not exceed 10 mg/10 mg once daily *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].*

There are no dosage adjustment recommendations for patients with mild and moderate renal impairment.

2.4 Dosage Modifications Due to Drug Interactions

Dosage Modifications Due to Drug Interactions

Table 1 displays dosage modifications for ROSZET due to drug interactions *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)].*

Table 1. ROSZET Dosage Modifications Due to Drug Interactions

Concomitantly Used Drug	**ROSZET Dosage Modifications (rosuvastatin/ezetimibe)**
Teriflunomide	Do not exceed ROSZET 10 mg/10 mg once daily.
Enasidenib	Do not exceed ROSZET 10 mg/10 mg once daily.
Capmatinib	Do not exceed ROSZET 10 mg/10 mg once daily.
Fostamatinib	Do not exceed ROSZET 20 mg/10 mg once daily.
Febuxostat	Do not exceed ROSZET 20 mg/10 mg once daily.
Tafamidis	Avoid concomitant use of tafamidis with ROSZET. If used concomitantly, initiate ROSZET at 5 mg/10 mg once daily and do not exceed ROSZET 20 mg/10 mg once daily.
Antiviral Medications	
• sofosbuvir/velpatasvir/voxilaprevir • ledipasvir/sofosbuvir	Concomitant use with ROSZET is not recommended.
• Simeprevir • dasabuvir/ombitasvir/paritaprevir/ritonavir • elbasvir/grazoprevir • sofosbuvir/velpatasvir • glecaprevir/pibrentasvir • atazanavir/ritonavir • lopinavir/ritonavir	Initiate ROSZET at 5 mg/10 mg once daily. Do not exceed ROSZET 10 mg/10 mg once daily.
Darolutamide	Do not exceed ROSZET 5 mg/10 mg once daily.
Regorafenib	Do not exceed ROSZET 10 mg/10 mg once daily.

3 DOSAGE FORMS AND STRENGTHS

ROSZET tablets are available as follows:

Strength	**Contents**	**Description**
5 mg/10 mg	rosuvastatin 5 mg/ezetimibe 10 mg	round pink biconvex tablets with “5” embossed on one side
10 mg/10 mg	rosuvastatin 10 mg/ezetimibe 10 mg	round pink biconvex tablets with “AL” embossed on one side
20 mg/10 mg	rosuvastatin 20 mg/ezetimibe 10 mg	round pink biconvex tablets with “II” embossed on one side
40 mg/10 mg	rosuvastatin 40 mg/ezetimibe 10 mg	round pink biconvex tablets with “77” embossed on one side

4 CONTRAINDICATIONS

ROSZET is contraindicated in patients with:

- Acute liver failure or decompensated cirrhosis.

- Hypersensitivity to rosuvastatin, ezetimibe, or any excipients in ROSZET. Hypersensitivity reactions including anaphylaxis, angioedema, and erythema multiforme have been reported *[see Adverse Reactions (6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy and Rhabdomyolysis

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

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 ROSZET dosage; Asian patients on ROSZET may be at higher risk for myopathy *[see Drug Interactions (7.1) and Use in Specific Populations (8.8)].* The myopathy risk is greater in patients taking ROSZET 40 mg/10 mg daily compared with lower ROSZET dosages.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

The concomitant use of ROSZET with cyclosporine or gemfibrozil is not recommended. ROSZET dosage modifications are recommended for patients taking certain antiviral medications, darolutamide, and regorafenib *[see Dosage and Administration (2.4)].* Niacin, fibrates, and colchicine may also increase the risk of myopathy and rhabdomyolysis *[see Drug Interactions (7.1)].*

Discontinue ROSZET if markedly elevated CK levels occur or myopathy is either diagnosed or suspected. Muscle symptoms and CK elevations may resolve if ROSZET is discontinued. Temporarily discontinue ROSZET 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 ROSZET dosage. Instruct patients to promptly report any unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

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 ROSZET if IMNM is suspected.

5.3 Hepatic Dysfunction

Increases in serum transaminases have occurred with rosuvastatin [*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. In a pooled analysis of placebo-controlled trials, increases in serum transaminases to more than three times the ULN occurred in 1.1% of patients taking rosuvastatin versus 0.5% of patients treated with placebo. Marked persistent increases of hepatic transaminases have also occurred with rosuvastatin.

There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin.

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 × 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.

Patients who consume substantial quantities of alcohol and/or have a history of liver disease may be at increased risk for hepatic injury.

Consider liver enzyme testing before ROSZET initiation and thereafter, when clinically indicated and consider withdrawal of ROSZET if increases in ALT or AST ≥3 × ULN persist. ROSZET 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 ROSZET.

5.4 Proteinuria and Hematuria

In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin treated patients. These findings were more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, consider a dose reduction for patients on ROSZET therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

5.5 Increases in HbA1c and Fasting Serum Glucose Levels

Increases in HbA1c and fasting serum glucose levels have been reported with statins, including rosuvastatin. Based on clinical trial data with rosuvastatin, in some instances these increases may exceed the threshold for the diagnosis of diabetes mellitus *[See Adverse Reactions (6.1)].* Optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- 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)]*
- Proteinuria and Hematuria *[see Warnings and Precautions (5.4)]*
- Increases in HbA1c and Fasting Serum Glucose Levels *[see Warnings and Precautions (5.5)]*

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.

Rosuvastatin

In double-blind, controlled (placebo- or active-controlled) clinical trials of rosuvastatin, 5,394 patients with primary hyperlipidemia were treated for a duration of up to 12 weeks. Adverse reactions reported in ≥2% of patients in placebo-controlled clinical studies and at a rate greater than placebo are shown in Table 2.

Table 2. Adverse Reactions Reported in ≥2% of Patients Treated with Rosuvastatin and Greater than Placebo in Placebo-Controlled Trials

Adverse Reactions	Placebo (N=382) %	Total Rosuvastatin 5 mg-40 mg (N=744) %
Headache	5.0	5.5
Nausea	3.1	3.4
Myalgia	1.3	2.8
Asthenia	2.6	2.7
Constipation	2.4	2.4

Other adverse reactions reported in clinical studies were abdominal pain, dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema), and pancreatitis.

In a double-blind, placebo-controlled trial with mean treatment duration of 1.7 years, 981 participants were treated with rosuvastatin 40 mg (n=700) or placebo (n=281). The most common adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 3.

Table 3. Adverse Reactions Occurring in ≥2% of Patients Treated with Rosuvastatin and Greater than Placebo

Adverse Reactions	Placebo (N=281) %	Rosuvastatin 40 mg (N=700) %
Myalgia	12.1	12.7
Arthralgia	7.1	10.1
Headache	5.3	6.4
Dizziness	2.8	4.0
Increased CPK	0.7	2.6
Abdominal pain	1.8	2.4
ALT >3x ULN[1]	0.7	2.2

1 Frequency recorded as abnormal laboratory value.

In a double-blind, placebo-controlled trial with mean treatment duration of 2 years, 17,802 participants were treated with rosuvastatin 20 mg (n=8,901) or placebo (n=8,901). There was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c >6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients.

Laboratory Tests

The following laboratory abnormalities have been reported in clinical studies of rosuvastatin: dipstick-positive proteinuria and microscopic hematuria; elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

Ezetimibe Monotherapy

In 10 double-blind, placebo-controlled clinical trials, 2,396 patients with primary hyperlipidemia (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 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 4.

Table 4: Adverse Reactions Occurring in ≥2% of Patients Treated with Ezetimibe and Greater than Placebo in Placebo-Controlled Trials

Adverse Reactions	Placebo (N=1,159) %	Ezetimibe (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

The incidence of consecutive elevations (≥3x ULN) in hepatic transaminase levels was similar between ezetimibe (0.5%) and placebo (0.3%).

Ezetimibe Combination with Statins
In 28 double-blind, controlled (placebo- or active-controlled) clinical trials, 11,308 patients with primary hyperlipidemia (48% female, 85% White, 7% Black or African American, 3% Asian, 5% other racs; 4% identified as Hispanic or Latino ethnicity) and elevated LDL-C were treated with ezetimibe concurrently with or added to ongoing statin therapy for a median treatment duration of 8 weeks (range 0 to 112 weeks). Clinical adverse reactions reported in ≥2% of patients treated with ezetimibe + statin and at an incidence greater than statin are shown in Table 5.

Table 5: Adverse Reactions Occurring in ≥2% of Patients Treated with Ezetimibe Coadministered with a Statin and at an Incidence Greater than Statin

Adverse Reactions	All Statins[1] (N=9361) %	Ezetimibe + All Statins[1] (N=2396) %
Nasopharyngitis	3.3	3.7
Myalgia	2.7	3.2
Upper respiratory tract infection	2.8	2.9
Arthralgia	2.4	2.6
Diarrhea	2.2	2.5
Back pain	2.3	2.4
Influenza	2.1	2.2
Pain in extremity	1.9	2.1
Fatigue	1.6	2.0

1 All Statins = all doses of statins

The incidence of consecutive increased transaminases (≥3x ULN) was higher in patients receiving ezetimibe administered with statins (1.3%) than in patients treated with statins alone (0.4%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rosuvastatin and ezetimibe. Because these reactions 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.

Rosuvastatin

Blood Disorders: thrombocytopenia

Hepatobiliary Disorders: hepatitis, jaundice, fatal and non-fatal hepatic failure

Musculoskeletal Disorders: arthralgia, rare reports of immune-mediated necrotizing myopathy associated with statin use

Nervous System Disorders: peripheral neuropathy, rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, and confusion) associated with the use of 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). 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, sleep disorders (including insomnia and nightmares)

Reproductive System and Breast Disorders: gynecomastia

Respiratory Disorders: interstitial lung disease

Skin and Subcutaneous Tissue Disorders: drug reaction with eosinophilia and systemic symptoms (DRESS), lichenoid drug eruption

Ezetimibe

Blood Disorders: thrombocytopenia

Gastrointestinal Disorders: abdominal pain; pancreatitis; nausea

Hepatobiliary Disorders: elevations in liver transaminases, including elevations more than 5 X 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

7 DRUG INTERACTIONS

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

Rosuvastatin is a substrate of CYP2C9 and transporters (such as OATP1B1, BCRP). Rosuvastatin plasma levels can be significantly increased with concomitant administration of inhibitors of CYP2C9 and transporters. Table 6 includes a list of drugs that increase the risk of myopathy and rhabdomyolysis when used concomitantly with ROSZET and instructions for preventing or managing them *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].*

Table 6: Drug Interactions that Increase the Risk of Myopathy and Rhabdomyolysis with ROSZET

Cyclosporine or Gemfibrozil	
Clinical Impact:	Cyclosporine increased rosuvastatin exposure 7-fold. In addition, ezetimibe and cyclosporine used concomitantly can increase exposure to both ezetimibe and cyclosporine. Gemfibrozil significantly increased

	rosuvastatin exposure and gemfibrozil may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of cyclosporine or gemfibrozil with ROSZET.
Intervention:	Avoid concomitant use of cyclosporine or gemfibrozil with ROSZET.
Anti-Viral Medications	
Clinical Impact:	Rosuvastatin plasma levels were significantly increased with concomitant administration of many anti-viral drugs, which increases the risk of myopathy and rhabdomyolysis.
Intervention:	Avoid concomitant use of sofosbuvir/velpatasvir/voxilaprevir and ledipasvir/sofosbuvir with ROSZET. In patients taking simeprevir, dasabuvir/ombitasvir/paritaprevir/ritonavir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, atazanavir/ritonavir, and lopinavir/ritonavir initiate with a dose of ROSZET 5 mg/10mg once daily, and do not exceed a dose of ROSZET 10 mg/10 mg once daily. No dose adjustment is needed for concomitant use with fosamprenavir/ritonavir or tipranavir/ritonavir. Monitor all patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward titration of either drug.
Teriflunomide	
Clinical Impact:	Teriflunomide increased rosuvastatin exposure more than 2.5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking teriflunomide, do not exceed a dose of ROSZET 10 mg/10 mg once daily.
Enasidenib	
Clinical Impact:	Enasidenib increased rosuvastatin exposure more than 2.4-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking enasidenib, do not exceed a dose of ROSZET 10 mg/10 mg once daily.
Capmatinib	
Clinical Impact:	Capmatinib increased rosuvastatin exposure more than 2.1-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking capmatinib, do not exceed a dose of ROSZET 10 mg/10 mg once daily.
Fostamatinib	
Clinical Impact:	Fostamatinib increased rosuvastatin exposure more than 2.0-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking fostamatinib, do not exceed a dose of ROSZET 20 mg/10 mg once daily.
Febuxostat	
Clinical Impact:	Febuxostat increased rosuvastatin exposure more than 1.9-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking febuxostat, do not exceed a dose of ROSZET 20 mg/10 mg once daily.
Tafamidis	
Clinical Impact:	Tafamidis significantly increased rosuvastatin exposure and tafamidis may cause myopathy when given alone. The risk of myopathy and

	rhabdomyolysis is increased with concomitant use of tafamidis with ROSZET.
Intervention:	Avoid concomitant use of tafamidis with ROSZET. If used concomitantly, initiate ROSZET at 5 mg/10 mg once daily and do not exceed a dose of ROSZET 20 mg/10 mg once daily. Monitor for signs of myopathy and rhabdomyolysis if used concomitantly with ROSZET.
Darolutamide	
Clinical Impact:	Darolutamide increased rosuvastatin exposure more than 5-fold. The risk of myopathy and rhabdomyolysis is increased with concomitant use.
Intervention:	In patients taking darolutamide, do not exceed a dose of ROSZET 5 mg/10 mg once daily.
Regorafenib	
Clinical Impact:	Regorafenib increased rosuvastatin exposure and may increase the risk of myopathy.
Intervention:	In patients taking regorafenib, do not exceed a dose of ROSZET 10 mg/10 mg once daily.
Fenofibrates (e.g., fenofibrate and fenofibric acid)	
Clinical Impact:	Fibrates may cause myopathy when given alone. The risk of myopathy and rhabdomyolysis is increased with concomitant use of fibrates with ROSZET.
Intervention:	Consider if the benefit of using fibrates concomitantly with ROSZET 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.
Niacin	
Clinical Impact:	Cases of myopathy and rhabdomyolysis have occurred with concomitant use of niacin with rosuvastatin.
Intervention:	Consider if the benefit of using niacin concomitantly with ROSZET 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 ROSZET
Intervention:	Consider if the benefit of using colchicine concomitantly with ROSZET 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.
Ticagrelor	
Clinical Impact:	Concomitant use of ROSZET and ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy. Cases of myopathy and rhabdomyolysis have been reported in patients using both products concomitantly. Cases have occurred more frequently in patients taking 40 mg of rosuvastatin.
Intervention:	In patients taking concomitant ticagrelor, especially those with additional risk factors for myopathy and rhabdomyolysis, monitor patients for signs and symptoms of myopathy, particularly during initiation of therapy and during upward dose titration of ROSZET.

7.2 Drug Interactions that Decrease the Efficacy of ROSZET

Table 7 presents drug interactions that may decrease the efficacy of ROSZET and instructions for preventing or managing them.

Table 7: Drug Interactions that Decrease the Efficacy of ROSZET

Bile Acid Sequestrants	
Clinical Impact:	Concomitant cholestyramine administration decreased the mean exposure of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding ezetimibe may be attenuated by coadminstration with cholestyramine. *[see Clinical Pharmacology (12.3)].*
Intervention:	In patients taking a bile acid sequestrant, administer ROSZET at least 2 hours before or at least 4 hours after the bile acid sequestrant.
Antacids	
Clinical Impact:	Concomitant aluminum and magnesium hydroxide combination antacid administration decreased the mean exposure of rosuvastatin 50% and total ezetimibe 4%. The incremental LDL-C reduction due to adding ROSZET may be attenuated by coadministration with antacid. *[see Clinical Pharmacology (12.3)].*
Intervention:	In patients taking antacid, administer ROSZET 2 hours before the antacid.

7.3 ROSZET Effects on Other Drugs

Table 8 presents ROSZET's effect on other drugs and instructions for preventing or managing them.

Table 8: ROSZET Effects on Other Drugs

Warfarin	
Clinical Impact:	Rosuvastatin significantly increased the INR in patients receiving coumarin anticoagulants *[see Clinical Pharmacology (12.3)].*
Intervention:	In patients taking warfarin, obtain an INR before starting ROSZET 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 ROSZET when pregnancy is recognized. Alternatively, consider the ongoing therapeutic needs of the individual patient. ROSZET decreases synthesis of cholesterol and possibly other biologically active substances derived from cholesterol; therefore, ROSZET may cause fetal harm when administered to pregnant patients 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 rosuvastatin use in pregnant women are insufficient to determine if there is a drug-associated risk of miscarriage *(see Data).* In animal reproduction studies, oral administration of rosuvastatin to pregnant rats and rabbits during organogenesis at doses equivalent to the maximum recommended human dose (MRHD) of 40 mg/day resulted in no adverse developmental effects *(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, oral administration of ezetimibe to pregnant rats and rabbits during organogenesis at doses 10 and 150 times, respectively, the MRHD resulted in no adverse developmental effects *(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 background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

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

Rosuvastatin

Rosuvastatin administration did not indicate a teratogenic effect in rats at ≤25 mg/kg/day or in rabbits ≤3 mg/kg/day (doses equivalent to the MRHD of 40 mg/day based on AUC and body surface area, respectively).

In female rats given 5, 15 and 50 mg/kg/day before mating and continuing through to gestation day 7 resulted in decreased fetal body weight (female pups) and delayed ossification at 50 mg/kg/day (10 times the human exposure at the MRHD dose of 40 mg/day based on AUC).

In pregnant rats given 2, 10 and 50 mg/kg/day of rosuvastatin from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred at 50 mg/kg/day (dose equivalent to 12 times the MRHD of 40 mg/day based body surface area).

In pregnant rabbits given 0.3, 1, and 3 mg/kg/day of rosuvastatin from gestation day 6 to day 18, decreased fetal viability and maternal mortality was observed at 3 mg/kg/day (dose equivalent to the MRHD of 40 mg/day based on body surface area).

Rosuvastatin crosses the placenta in rats and rabbits and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma

concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18.

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 embryolethality at any dose tested (250, 500, 1,000 mg/kg/day) at exposures equivalent to 10 and 150 times the clinical exposure, based on AUC, in rats and rabbits. 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). 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 1000 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 (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.

8.2 Lactation

Risk Summary
Limited data from case reports in published literature indicate that rosuvastatin is present in human milk. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Statins, including ROSZET, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol and may cause harm to the breastfed infant.

There is no information about the presence of ezetimibe in human milk. Ezetimibe is present in rat milk *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. There is no information about the effects of ezetimibe on the breastfed infant or the effects of ezetimibe on milk production.

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 ROSZET *[see Use in Specific Populations (8.1), 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.

8.4 Pediatric Use
The safety and effectiveness of ROSZET have not been established in pediatric patients.

8.5 Geriatric Use
Advanced age (≥65 years) is a risk factor for ROSZET-associated myopathy and rhabdomyolysis. Dose selection for an elderly patient should be cautious, recognizing the greater frequency of decreased hepatic, renal, or cardiac function; of concomitant disease or other drug therapy; and the higher risk of myopathy. Monitor geriatric patients receiving ROSZET for the increased risk of myopathy *[see Warnings and Precautions (5.1)].*

Rosuvastatin
Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years of age and older, and 698 (6.8%) were 75 years of age and older.

Ezetimibe
Of the 2,396 patients who received ezetimibe monotherapy in clinical studies, 669 (28%) were 65 years of age and older, and 111 (5%) were 75 years of age and older. Of the 11,308 patients who received ezetimibe + statin in clinical studies, 3,587 (32%) were 65 and older, and 924 (8%) were 75 and older. No overall differences in safety and effectiveness were observed between patients 65 years of age and older and younger patients. No clinically meaningful differences in the pharmacokinetics of ezetimibe were observed in geriatric patients compared to younger adult patients *[See Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment
Renal impairment is a risk factor for myopathy and rhabdomyolysis. Monitor patients with renal impairment for development of myopathy. In patients with severe renal impairment not on hemodialysis, the recommended starting dosage is 5 mg/10 mg daily and should not exceed 10 mg/10 mg daily *[see Dosage and Administration (2.5) and Warnings and Precautions (5.1)].*

Rosuvastatin
Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CLcr≥30 mL/min/1.73 m^2). Exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CLcr<30 mL/min/1.73 m^2) who are not receiving hemodialysis *[see Clinical Pharmacology (12.3)].*

Ezetimibe
No dosage adjustment of ezetimibe is necessary in patients with renal impairment.

8.7 Hepatic Impairment
ROSZET is contraindicated in patients with acute liver failure or decompensated cirrhosis *[see Contraindications (4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)]*.

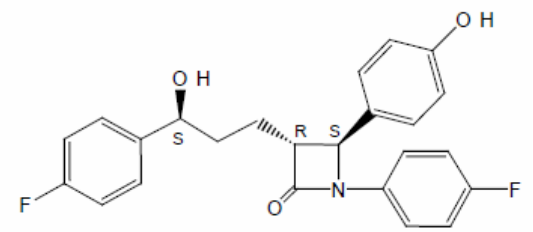
8.8 Asian Patients
Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with White controls. Adjust the ROSZET dosage in Asian patients *[see Dosage and Administration (2.2)]*

10 OVERDOSAGE
No specific treatments of over dosage with ROSZET are known. Hemodialysis does not significantly enhance clearance of rosuvastatin. In the event of overdose, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

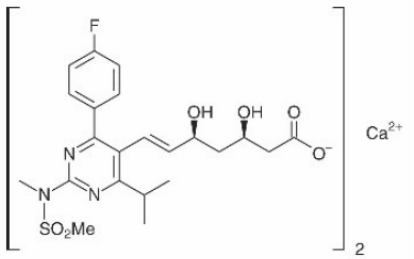
11 DESCRIPTION

ROSZET tablets contain rosuvastatin calcium and ezetimibe. Rosuvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA)-reductase inhibitor. Ezetimibe is a dietary cholesterol absorption inhibitor.

The chemical name of ezetimibe is (3R,4S)-1-(p-Fluorophenyl)-3-[(3S)-3-(p-fluorophenyl)-3-hydroxypropyl]-4-(p-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.43 $g.mol^{-1}$. Ezetimibe is a white, crystalline powder, which is insoluble in water. Its structural formula is:



The chemical name for rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2[methyl(methyl sulfonyl)amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt to [S-[R*,S*-(E)]]-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid, calcium salt (2:1). The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$ and the molecular weight is 1,001.14 $g.mol^{-1}$. Rosuvastatin calcium is a white amorphous powder that is sparingly soluble in water and methanol, and slightly soluble in ethanol. Rosuvastatin calcium is a hydrophilic compound with a partition coefficient (octanol/water) of 0.13 at pH of 7.0. Its structural formula is:



ROSZET tablets 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, and 40 mg/10 mg contain the equivalent of 5, 10, 20, and 40 mg rosuvastatin (provided as rosuvastatin calcium 5.2, 10.4, 20.8, and 41.7 mg) and 10 mg ezetimibe. Each film-coated tablet of ROSZET contains the following inactive ingredients: pregelatinized starch, microcrystalline cellulose, meglumine, dibasic calcium phosphate dihydrate , crospovidone, colloidal silicon dioxide, sodium stearyl fumarate, mannitol, sodium lauryl sulfate, croscarmellose sodium, povidone, ferric oxide, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, polyethylene glycol, and ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rosuvastatin

Rosuvastatin is an inhibitor of HMG CoA-reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol.

Ezetimibe

Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine.

The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.

12.2 Pharmacodynamics

Rosuvastatin

Inhibition of HMG-CoA reductase by rosuvastatin accelerates the expression of LDL-receptors, followed by the uptake of LDL-C from blood to the liver, leading to a decrease in plasma LDL-C and total cholesterol. Sustained inhibition of cholesterol synthesis in the liver also decreases levels of very-low-density lipoproteins. The maximum LDL-C reduction of rosuvastatin is usually achieved by 4 weeks and is maintained after that.

Ezetimibe

Ezetimibe 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 trial 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 (in a trial of 113 patients) and did not impair adrenocortical steroid hormone production (in a trial of 118 patients). The maximum therapeutic response of ezetimibe is generally achieved within 2 weeks and is maintained during chronic therapy.

12.3 Pharmacokinetics

Absorption

Rosuvastatin

In clinical pharmacology studies in males, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both Cmax and AUC increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%.The AUC of rosuvastatin does not differ following evening or morning drug administration.

Administration of rosuvastatin with food did not affect the AUC of rosuvastatin.

Ezetimibe

After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). After a single 10-mg dose of ezetimibe to fasted adults, mean ezetimibe peak plasma concentrations (Cmax) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours (Tmax). Ezetimibe-glucuronide mean Cmax values of 45 to 71 ng/mL were achieved between 1 and 2 hours (Tmax). There was no substantial deviation from dose proportionality between 5 and 20 mg. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as ezetimibe 10-mg tablets. The Cmax value of ezetimibe was increased by 38% with consumption of high-fat meals.

Distribution

Rosuvastatin

Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin

is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

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

Elimination
Metabolism

Rosuvastatin
Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 \ 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of the parent compound. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by the parent compound.
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.

Excretion
Rosuvastatin
Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

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.

Specific Populations
Geriatric Patients
Rosuvastatin
There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ≥65 years).

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.

Male and Female Patients

Rosuvastatin

There were no differences in plasma concentrations of rosuvastatin between males and females.

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.

Racial or Ethnic Groups

Rosuvastatin

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among White, Hispanic or Latino, and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a White control group. *[See Dosage and Administration (2.1) and Specific Populations (8.8).]*

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

Rosuvastatin

Mild to moderate renal impairment (CL_{cr} ≥30 mL/min/1.73 m^2) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CL_{cr} <30 mL/min/1.73 m^2) not receiving hemodialysis compared with healthy subjects (CL_{cr}>80 mL/min/1.73 m^2). Steady-state plasma concentrations of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CL_{cr}≤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).

Patients with Hepatic Impairment

Rosuvastatin

In patients with chronic alcohol liver disease, plasma concentrations of rosuvastatin were modestly increased. In patients with Child-Pugh A disease, C_{max} and AUC were increased by 60% and 5%, respectively, as compared with patients with normal liver function. In patients with Child-Pugh B disease, C_{max} and AUC were increased 100% and 21%, respectively, compared with patients with normal liver function *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

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 *[see Contraindications (4) and Warnings and Precautions (5.2), and Specific Populations (8.7)].*

Drug Interaction Studies

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

Cytochrome P450

Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter organic anion-transporting polyprotein 1B1 (OATP1B1) and efflux transporter breast cancer resistance protein (BCRP). Concomitant administration of ROSZET with medications that are inhibitors of these transporter proteins (e.g. cyclosporine, certain HIV protease inhibitors) *[see Dosage and Administration (2.4) and Drug Interactions (7.1)]* and ticagrelor *[see Drug Interactions (7.1)]* may result in increased rosuvastatin plasma concentrations.

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.

Rosuvastatin

Table 9: Effect of Coadministered Drugs on Rosuvastatin Systemic Exposure

Coadministered drug and dosing regimen	**Rosuvastatin**		
		Mean Ratio (ratio with/without coadministered drug) No Effect=1.0	
	Dose (mg)[1]	**Change in AUC**	**Change in C_{max}**
Sofosbuvir/velpatasvir/voxilaprevir (400 Mg/100 mg/100 mg) + Voxilaprevir (100 mg) QD for 15 days	10 mg single dose	7.39[2] (6.68 to 8.18)[3]	18.88[2] (16.23 to 21.96)[3]
Cyclosporine – stable dose required (75 mg – 200 mg BID)	10 mg QD for 10 days	7.1[2]	11[2]
Darolutamide 600 mg BID, 5 days	5 mg, single dose	5.2[2]	~5[2]
Regorafenib 160 mg OD, 14 days	5 mg single dose	3.8[2]	4.6[2]
Atazanavir/ritonavir combination 300 mg/100 mg QD for 8 days	10 mg	3.1[2]	7[2]
Simeprevir 150 mg QD, 7 days	10 mg, single dose	2.8[2] (2.3 to 3.4)[3]	3.2[2] (2.6 to 3.9)[3]
Velpatasvir 100 mg once daily	10 mg single dose	2.69[2] (2.46 to 2.94)[3]	2.61[2] (2.32 to 2.92)[3]
Ombitasvir 25 mg/paritaprevir 150 mg/ ritonavir 100 mg + dasabuvir 400 mg BID	5 mg single dose	2.59[2] (2.09 to 3.21)[3]	7.13[2] (5.11 to 9.96)[3]
Teriflunomide	Not available	2.51[2]	2.65[2]
Enasidenib 100 mg QD, 28 days	10 mg, single dose	2.44	3.66
Elbasvir 50 mg/grazoprevir 200 mg QD	10 mg single dose	2.26[2] (1.89 to 2.69)[3]	5.49[2] (4.29 to 7.04)[3]
Glecaprevir 400 mg/pibrentasvir 120 mg QD	5 mg once daily	2.15[2] (1.88 to 2.46)[3]	5.62[2] (4.80 to 6.59)[3]
Lopinavir/ritonavir combination 400 mg/100 mg BID for 17 days	20 mg QD for 7 days	2.1[2] (1.7 to 2.6)[3]	5[2] (3.4 to 6.4)[3]
Capmatinib 400 mg BID	10 mg, single dose	2.08[2] (1.56 to 2.76)[3]	3.04[2] (2.36 to 3.92)[3]
Fostamatinib 100 mg BID	20 mg, single dose	1.96[2] (1.77 to 2.15)[3]	1.88[2] (1.69 to 2.09)[3]
Febuxostat 120 mg QD for 4 days	10 mg, single dose	1.9[2] (1.5 to 2.5)[3]	2.1[2] (1.8 to 2.6)[3]
Gemfibrozil 600 mg BID for 7 days	80 mg	1.9[2] (1.6 to 2.2)[3]	2.2[2] (1.8 to 2.7)[3]
Tafamidis 61 mg BID on Days 1 & 2, followed by QD on Days 3 to 9	10 mg	1.97[2] (1.68 to 2.31)[3]	1.86[2] (1.59 to 2.16)[3]
Eltrombopag 75 mg QD, 5 days	10 mg	1.6 (1.4 to 1.7)[3]	2 (1.8 to 2.3)[3]
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg QD for 7 days	1.5 (1.0 to 2.1)[3]	2.4 (1.6 to 3.6)[3]
Tipranavir/ritonavir combination 500 mg/200 mg BID for 11 days	10 mg	1.4 (1.2 to 1.6)[3]	2.2 (1.8 to 2.7)[3]
Dronedarone 400 mg BID	10 mg	1.4	
Itraconazole 200 mg QD, 5 days	10 mg or 80 mg	1.4 (1.2 to 1.6)[3] 1.3 (1.1 to 1.4)[3]	1.4 (1.2 to 1.5)[3] 1.2 (0.9 to 1.4)[3]

Ezetimibe 10 mg QD, 14 days	10 mg QD for 14 days	1.2 (0.9 to 1.6)[3]	1.2 (0.8 to 1.6)[3]
Fosamprenavir/ritonavir 700 mg/100 mg BID for 7 days	10 mg	1.1	1.5
Fenofibrate 67 mg TID for 7 days	10 mg	↔	1.2 (1.1 to 1.3)[3]
Rifampicin 450 mg QD, 7 days	20 mg	↔	
Aluminum & magnesium hydroxide combination antacid Administered simultaneously Administered 2 hours apart	 40 mg 40 mg	 0.5[2] (0.4 to 0.5)[3] 0.8 (0.7 to 0.9)[3]	 0.5[2] (0.4 to 0.6)[3] 0.8 (0.7 to 1.0)[3]
Ketoconazole 200 mg BID for 7 days	80 mg	1.0 (0.8 to 1.2)[3]	1.0 (0.7 to 1.3)[3]
Fluconazole 200 mg QD for 11 days	80 mg	1.1 (1.0-1.3)[3]	1.1 (0.9-1.4)[3]
Erythromycin 500 mg QID for 7 days	80 mg	0.8 (0.7 to 0.9)[3]	0.7 (0.5 to 0.9)[3]

QD= Once daily, BID= Twice daily, TID= Three times daily, QID= Four times daily

[1] Single dose unless otherwise noted.
[2] Clinically significant *[See Dosage and Administration (2), Warnings and Precautions (5), and Drug Interactions (7)]*
[3] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7 = 30% decrease,11=11 fold increase in exposure)

Table 10: Effect of Rosuvastatin Coadministration on Systemic Exposure to Other Drugs

Rosuvastatin Dosage Regimen	**Coadministered Drug**		
		Mean Ratio (ratio with/without coadministered drug) No Effect=1.0	
	Name and Dose	**Change in AUC**	**Change in C_{max}**
40 mg QD for 10 days	Warfarin[1] 25 mg single dose	R- Warfarin 1.0 (1.0 to 1.1)[2] S-Warfarin 1.1 (1.0 to 1.1)[2]	R-Warfarin 1.0 (0.9 to 1.0)[2] S-Warfarin 1.0 (0.9 to 1.1)[2]
40 mg QD for 12 days	Digoxin 0.5 mg single dose	1.0 (0.9 to 1.2)[2]	1.0 (0.9 to 1.2)[2]
40 mg QD for 28 days	Oral Contraceptive (ethinyl estradiol 0.035 mg & norgestrel 0.180, 0.215 and 0.250 mg) QD for 21 Days	EE 1.3 (1.2 to 1.3)[2] NG 1.3 (1.3 to 1.4)[2]	EE 1.3 (1.2 to 1.3)[2] NG 1.2 (1.1 to 1.3)[2]

EE = ethinyl estradiol, NG = norgestrel, QD= Once daily
[1] Clinically significant pharmacodynamic effects *[see Drug Interactions (7)]*
[2] Mean ratio with 90% CI (with/without coadministered drug, e.g., 1= no change, 0.7=30% decrease, 11=11-fold increase in exposure)

Ezetimibe

Table 11: Effect of Co-Administered Drugs on Total Ezetimibe

Coadministered Drug and Dosing Regimen	Total Ezetimibe[4]	
	Change in AUC	Change in Cmax
Cyclosporine-stable dose required (75-150 mg BID)[1,2]	↑240%	↑290%
Fenofibrate, 200 mg QD, 14 days[2]	↑48%	↑64%
Gemfibrozil, 600 mg BID, 7 days[2]	↑64%	↑91%
Cholestyramine, 4 g BID, 14 days[2]	↓55%	↓4%
Aluminum & magnesium hydroxide combination antacid, single dose[3]	↓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%

[1] 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/1.73m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects.

[2] *See Drug Interactions (7)*

[3] Supralox®, 20 mL

[4] Based on 10-mg dose of ezetimibe

Table 12: 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 Cmax 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[1]	10 mg QD, 7 days	↓1%	↓11%
Ethinyl estradiol and levonorgestrel, QD, 21 days	10 mg QD, Days 8-14 of 21 day 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[1]	10 mg QD, 14 days	↑11%	↑7%
Cyclosporine, 100 mg single dose Day 7[1]	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%

[1] *See Drug Interactions (7)*

12.5 Pharmacogenomics

Disposition of rosuvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T > C). The frequency of this genotype (i.e., SLCO1B1 521T>C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on rosuvastatin is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal carcinogenicity or fertility studies have been conducted with the combination of rosuvastatin and ezetimibe.

Rosuvastatin

In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses.

In a 107-week carcinogenicity study in mice given 10, 60, or 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times the human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses.

Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test.

In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times the human exposure at 40 mg/day based on AUC). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatidic giant cells were seen. Spermatidic giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times the human exposure at 40 mg/day based on body surface area. Similar findings have been seen with other drugs in this class.

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).

14 CLINICAL STUDIES

14.1 Primary Hyperlipidemia

ROSZET reduces total-C, LDL-C, Apo B, and non-HDL-C in adults with hyperlipidemia.

Rosuvastatin monotherapy
In a multicenter, double-blind, placebo-controlled, dose-ranging trial in patients with hyperlipidemia, rosuvastatin given as a single daily dose for 6 weeks significantly reduced Total-C, LDL-C, non-HDL-C and Apo B, across the dose range (see Table 13)

Table 13. Dose-Response of Rosuvastatin Monotherapy in Patients with Hyperlipidemia (Adjusted Mean % Change from Baseline at Week 6)

Dose	N	Total-C	LDL-C	Non-HDL-C	Apo B	TG	HDL-C
Placebo	13	-5	-7	-7	-3	-3	3
Rosuvastatin 5 mg	17	-33	-45	-44	-38	-35	13
Rosuvastatin 10 mg	17	-36	-52	-48	-42	-10	14
Rosuvastatin 20 mg	17	-40	-55	-51	-46	-23	8
Rosuvastatin 40 mg	18	-46	-63	-60	-54	-28	10

Ezetimibe added to ongoing statin therapy
In a multicenter, double-blind, placebo-controlled, 8-week trial, 769 patients with primary hyperlipidemia, known coronary heart disease or multiple cardiovascular risk factors who were already receiving statin monotherapy, but who had not met their NCEP ATP II target LDL-C goal were randomized to receive either ezetimibe or placebo in addition to their ongoing statin.

Ezetimibe, added to ongoing statin therapy, significantly lowered total-C, LDL-C, Apo B, non-HDL-C, and TG, and increased HDL-C compared with a statin administered alone (see Table 14). LDL-C reductions induced by ezetimibe were generally consistent across all statins.

Table 14: Response to Addition of Ezetimibe to Ongoing Statin Therapy[1] in Patients with Hyperlipidemia (Mean[2] % Change from Treated Baseline[3])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	Non-HDL-C	TG	HDL-C
Ongoing Statin + Placebo[4]	390	-2	-4	-3	-3	-3	+1
Ongoing Statin + Ezetimibe[4]	379	-17	-25	-19	-23	-14	+3

1 Patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)

2 For triglycerides, median % change from baseline

3 Baseline – on a statin alone

4 Ezetimibe + statin significantly reduced total-C, LDL-C, Apo B, non-HDL-C, and TG and increased HDL-C compared to statin alone

14.2 HoFH

Rosuvastatin monotherapy

Dose-Titration Study: In an open-label, forced-titration study, homozygous FH patients (n=40) were evaluated for their response to rosuvastatin 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%. In the 27 patients with at least a 15% reduction in LDL-C, the mean LDL-C reduction was 30% (median 28% reduction). Among 13 patients with an LDL-C reduction of <15%, 3 had no change or an increase in LDL-C. Reductions in LDL-C of 15% or greater were observed in 3 of 5 patients with known receptor negative status.

Ezetimibe monotherapy

A study was conducted to assess the efficacy of ezetimibe in the treatment of HoFH. This double-blind, randomized, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg). Patients were randomized to one of three treatment groups: atorvastatin or simvastatin (80 mg), ezetimibe administered with atorvastatin or simvastatin (40 mg), or ezetimibe administered with atorvastatin or simvastatin (80 mg). Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine, ezetimibe was dosed at least 4 hours before or after administration of resins. Mean baseline LDL-C was 341 mg/dL in those patients randomized to atorvastatin 80 mg or simvastatin 80 mg alone and 316 mg/dL in the group randomized to ezetimibe plus atorvastatin 40 or 80 mg or simvastatin 40 or 80 mg. Ezetimibe, administered with atorvastatin or simvastatin (40 and 80 mg statin groups, pooled), significantly reduced LDL-C (21%) compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg (7%). In those treated with ezetimibe plus 80 mg atorvastatin or with ezetimibe plus 80 mg simvastatin, LDL-C was reduced by 27%.

16 HOW SUPPLIED/STORAGE AND HANDLING

ROSZET Tablets are supplied as follows:

Strength (Contents)	Description	Container	NDC
5 mg/10 mg (rosuvastatin 5 mg and ezetimibe 10 mg)	round pink biconvex tablets with "5" embossed on one side	Bottle of 30 tablets and one 1 g desiccant	70661-001-30
10 mg/10 mg (rosuvastatin 10 mg and ezetimibe 10 mg)	round pink biconvex tablets with "AL" embossed on one side	Bottle of 30 tablets and one 1 g desiccant	70661-002-30
20 mg/10 mg (rosuvastatin 20 mg and ezetimibe 10 mg)	round pink biconvex tablets with "II" embossed on one side	Bottle of 30 tablets and one 1 g desiccant	70661-003-30
40 mg/10 mg (rosuvastatin 40 mg and ezetimibe 10 mg)	round pink biconvex tablets with "77" embossed on one side	Bottle of 30 tablets and one 1 g desiccant	70661-004-30

Store at controlled room temperature (USP), 20°C to 25 ºC (68°F to 77 ºF) [see USP Controlled Room Temperature]. Store in the original container to protect from light. Protect from moisture. Once the bottle has been opened, use the tablets within 30 days.

Dispense in original container to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myopathy and Rhabdomyolysis

Advise patients that ROSZET may cause myopathy and rhabdomyolysis. Inform patients that the risk is also increased when taking certain types of medication 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 ROSZET 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 ROSZET. Encourage patients to optimize lifestyle measures, including regular exercise, maintaining a healthy body weight, and making healthy food choices *[see Warnings and Precautions (5.5)].*

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 ROSZET should be discontinued *[see Use in Specific Populations (8.1)].*

Lactation

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

Concomitant Use of Antacids

When taking ROSZET with an aluminum and magnesium hydroxide combination antacid, administer ROSZET at least 2 hours before the antacid *[see Drug Interactions (7.2)].*

Administration Instructions

Advise patients to swallow tablets whole. Do not crush, dissolve, or chew tablets. If a dose is missed, advise patients not to take an extra dose. Just resume the usual schedule.

Manufactured by:
Piramal Enterprise Limited,
Plot No. 67-70, Sector 2, Dist. Dhar, Pithampur,
Madhya Pradesh 454775, India

Manufactured for:
Althera Pharmaceuticals LLC
1201 N Orange St, Suite 712,
Wilmington DE 19801
USA

ROSZET is a trademark of Althera.

U.S. Patent No. 9,763,885, and 10,376,470
Ref: AL-320-000-3

Patient Information
ROSZET® (ROS-zett)
(rosuvastatin and ezetimibe)
tablets, for oral use

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

What is ROSZET?

ROSZET is a prescription medicine that contains two medicines, rosuvastatin and ezetimibe, to reduce cholesterol.

ROSZET is used along with:

- Diet to lower the level of low-density lipoprotein (LDL-C) cholesterol or "bad" cholesterol in adults with primary hyperlipidemia
- 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).

Pediatric use information is approved for Organon & Co.'s ZETIA (ezetimibe) tablets. However, due to Organon & Co.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

Do not take ROSZET if you:

- have liver problems.
- are allergic to ezetimibe, rosuvastatin or any of the ingredients in ROSZET. See the end of this leaflet for complete list of ingredients in ROSZET.

Before you take ROSZET, 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.
- drink more than 2 glasses of alcohol daily.
- have thyroid problems.
- are of Asian descent.
- are pregnant or think you may be pregnant, or are planning to become pregnant. If you become pregnant while taking ROSZET, call your healthcare provider right away to discuss your ROSZET treatment.
- are breast feeding. ROSZET can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take ROSZET. Do not breastfeed while taking ROSZET.

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 ROSZET if another healthcare provider increases the dose of another medicine you are taking.

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

- coumarin anticoagulants (medicines that prevent blood clots, such as warfarin)
- bile acid sequestrants (medicine for lowering LDL-C)
- antacids (medicines you take for heartburn that contain aluminum and magnesium hydroxide)

Taking ROSZET 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)
- anti-viral medicines including certain HIV or hepatitis C virus drugs such as:
    - lopinavir, ritonavir, fosamprenavir, tipranavir, atazanavir, simeprevira
    - combination of
        - sofosbuvir/velpatasvir/voxilaprevir
        - dasabuvir/ombitasvir/paritaprevir/ritonavir
        - elbasvir/grazoprevir
        - sofosbuvir/velpatasvir
        - glecaprevir/pibrentasvir **and**
    - all other combinations with ledipasvir including ledipasvir/sofosbuvir
- gemfibrozil (a fibric acid medicine for lowering cholesterol)
- teriflunomide (a medicine used to treat relapsing remitting multiple sclerosis)
- enasidenib (a medicine used to treat acute myeloid leukemia)
- capmatinib (a medicine for the treatment of non-small cell lung cancer)
- fostamatinib (a medicine used to treat low platelet counts)
- febuxostat (a medicine used to treat and prevent high blood levels of uric acid)
- tafamidis [used to treat cardiomyopathy (enlarged and thickened heart muscle)]

- darolutamide (a medicine for the treatment of prostate cancer)
- regorafenib (a medicine used to treat cancer of the colon and rectum)
- fibric acid derivatives (such as fenofibrate)
- niacin or nicotinic acid
- colchicine (a medicine used to treat gout)
- ticagrelor (helps reduce the chance of a blood clot formation that can block a blood vessel)

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure. Know all of the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get new medicine.

How should I take ROSZET?

- Take ROSZET exactly as your healthcare provider tells you to take it.
- Take ROSZET, by mouth, 1 time each day, with or without food.
- Tablets should be swallowed whole. Do not crush, dissolve, or chew tablets.
- If you miss a dose of ROSZET, take your next dose at your normal scheduled time. **Do not take an extra dose of ROSZET.**
- **Do not** change your dose or stop ROSZET without talking to your healthcare provider, even if you are feeling well.
- Your healthcare provider may do blood tests to check your cholesterol levels before and during your treatment with ROSZET. Your healthcare provider may change your dose of ROSZET if needed.
- While taking ROSZET, 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 ROSZET at least 2 hours before or 4 hours after you take the bile acid sequestrant.
- If you take a medicine called an antacid that contains a combination of aluminum and magnesium hydroxide, take ROSZET at least 2 hours before you take the antacid.
- 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 are the possible side effects of ROSZET?
ROSZET 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 causes 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 have a fever or feel more tired than usual, while you take ROSZET.
    - you have muscle problems that do not go away even after your healthcare provider has told you to stop taking ROSZET. 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 ROSZET (see "**Especially tell your healthcare provider if you take")**
- are 65 years of age or older
- are of Asian descent
- have thyroid problems (hypothyroidism) that are not controlled
- have kidney problems
- are taking higher doses of ROSZET

- **Liver problems.** Your healthcare provider may do blood tests to check your liver before you start taking ROSZET and if you have symptoms of liver problems while you take ROSZET. 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
- **Protein and blood in the urine**. ROSZET may cause you to have protein and blood in your urine. If you develop protein or blood in your urine, your healthcare provider may decrease your dose of ROSZET.
- **Increase in blood sugar (glucose) levels**. ROSZET may cause an increase in your blood sugar levels.

The most common side effects of ROSZET include:

- headache
- weakness
- diarrhea
- pain (back, hands, legs)
- nausea
- constipation
- joint pain
- tiredness
- muscle aches and pains
- runny nose and sore throat
- common cold and flu

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of ROSZET. For more information, ask your healthcare provider or pharmacist.
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 ROSZET?

- Store ROSZET at room temperature between 68°F to 77°F (20°C to 25°C) in the original bottle.
- Protect ROSZET bottle from light, moisture, or humidity.
- After opening the bottle, use the tablets within 30 days.

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

General information about the safe and effective use of ROSZET.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use ROSZET for a condition for which it was not prescribed. Do not give ROSZET to other people, even if they have the same medical condition that you have. It may harm them.

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

What are the ingredients in ROSZET?

Active ingredients: ezetimibe and rosuvastatin

Inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, crospovidone, dibasic calcium phosphate dihydrate, ferric oxide, magnesium stearate, mannitol, meglumine, microcrystalline cellulose, povidone, pregelatinized starch, sodium lauryl sulfate and sodium stearyl fumarate. In addition, the tablet film coating contains the following inactive ingredients: ferric oxide, hypromellose, polyethylene glycol and titanium dioxide.

Manufactured by:
Piramal Enterprise Limited,
Plot No. 67-70, Sector 2, Dist. Dhar, Pithampur,
Madhya Pradesh 454775, India

Manufactured for:
Althera Pharmaceuticals LLC
1201 N Orange St, Suite 712,
Wilmington DE 19801
USA
U.S. Patent No. 9,763,885, and 10,376,470

Ref: AL-320-000-3

For more information, go to www.ROSZET.COM

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 08/2024