NEW DRUG APPROVAL

Brand Name	Roszet®
Generic Name	rosuvastatin and ezetimibe
Drug Manufacturer	Althera Pharmaceuticals LLC

New Drug Approval

FDA Approval Date: March 23, 2021

Review Designation: Standard

Type of Review: Type 4 - New Combination, New Drug Application (NDA) 213072

Dispensing Restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hyperlipidemia is a condition that incorporates various genetic and acquired disorders that describe elevated lipid levels within the human body. Hyperlipidemia is extremely common, especially in the Western hemisphere, but also throughout the world. Alternatively, a more objective definition describes hyperlipidemia as low-density lipoprotein (LDL), total cholesterol, triglyceride levels, or lipoprotein levels greater than the 90th percentile in comparison to the general population, or an HDL level less than the 10th percentile when compared to the general population. Lipids typically include cholesterol levels, lipoproteins, chylomicrons, VLDL, LDL, apolipoproteins, and HDL.

There are over three million adults throughout the United States and Europe that currently have a diagnosis of hyperlipidemia, and that number continues to rise at a drastic pace. Hyperlipidemia is typically a chronic, progressive disease process that demands lifestyle and dietary changes, with the potential need for additional lipid-lowering medications. The degree of hyperlipidemia is highest in patients with premature coronary artery disease (CAD), defined as CAD arising in males before age 55 to 60 years and females before age 65 years. Under the prior specified circumstances, the incidence of hyperlipidemia is around 75-85%, opposed to roughly 40 to 48% in the control population of comparable age, but without the presence of premature coronary artery disease.

Estimates are that over 50% of American adults have elevated LDL levels, and it is speculated that under 35% of those patients adequately manage their high LDL levels, clearly depicting an undertreated disease. Per the JAMA Network, "Prevalence of dyslipidemia was significantly greater among whites than blacks (women, 64.7% vs. 49.5%; and men, 78.4% vs. 56.7%; P<.001 for both) and amongst men than women (P≤.02 in every ethnic group)." Intuitively, in countries with lower overall rates of obesity and saturated fat consumption, the prevalence of hyperlipidemia and subsequent coronary artery disease is lower, when contrasted to rates in Europe and throughout the United States.

Children under two years of age, if underweight or obese, may develop secondary (non-genetic) pediatric hyperlipidemia.

Efficacy

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

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Rosuvastatin monotherapy

In a multicenter, double-blind, placebo-controlled, dose-ranging study in patients with hyperlipidemia, rosuvastatin given as a single daily dose for 6 weeks significantly reduced Total-C, LDL-C, non-HDLC, and Apo B, across the dose range.

Table: 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

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 (Table 13). LDL-C reductions induced by ezetimibe were generally consistent across all statins.

Table: Response to Addition of Ezetimibe to Ongoing Statin Therapy1 in Patients with Hyperlipidemia (Mean2 % Change from Treated Baseline3)

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

Safety

ADVERSE EVENTS

Most common adverse reactions for:

- Rosuvastatin (incidence >2% and greater than placebo) are headache, nausea, myalgia, arthralgia, dizziness, asthenia, constipation, and abdominal pain.
- Ezetimibe (incidence >2% and greater than placebo) are upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity, fatigue, and influenza.
- 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, pain in extremity, and fatigue.

WARNINGS & 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. 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.

- Immune-Mediated Necrotizing Myopathy (IMNM): Rare reports of IMNM, an autoimmune myopathy, have been reported with statin use.
- 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 tests before initiating therapy and as clinically indicated thereafter. If serious hepatic injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs, promptly discontinue Roszet®

CONTRAINDICATIONS

- Active liver failure or decompensated cirrhosis.
- Hypersensitivity to any component of Roszet®

Clinical Pharmacology

MECHANISMS OF ACTION

Rosuvastatin

Rosuvastatin is an inhibitor of HMG CoA-reductase, the rate-limiting enzyme that converts 3-hydroxy3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. In in vivo and in vitro studies, rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.

Ezetimibe

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.

Dose & Administration

ADULTS

40 mg/day PO rosuvastatin and 10 mg/day PO ezetimibe.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

CrCl 30 mL/min or greater: No dosage adjustment needed.

HEPATIC IMPAIRMENT

Rosuvastatin; ezetimibe is contraindicated in patients with acute liver injury or decompensated cirrhosis.

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Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets (rosuvastatin/ezetimibe): 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg.