Ezetimibe/Simvastatin

Jestamivam

Tablets

b

Trade name: Jestamivam 10/40 & Jestamivam 10/80 **Dosage Form:** Tablets.

Active Ingredients: Ezetemibe 10 mg & Simvastatin 40 mg, Ezetemibe 10 mg & simvastatin 80 mg.

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:*** JESTAMIVAM 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): JESTAMIVAM 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 JESTAMIVAM on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established. JESTAMIVAM has not been studied in Fredrickson type I, III, IV, and V dyslipidemias.

2.Dosage and administration:*2.1.Recommended Dosing:* The dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. JESTAMIVAM should be taken as a single daily dose in the evening, with or without food. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day. After initiation or titration of JESTAMIVAM, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed.

2.2.Patients with Homozygous Familial Hypercholesterolemia: The recommended dosage for patients with homozygous familial hypercholesterolemia is JESTAMIVAM 10/40 mg/day or 10/80 mg/day in the evening. JESTAMIVAM 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.Patients with Hepatic Impairment: No dosage adjustment is necessary in patients with mild hepatic impairment [see Warnings and Precautions (5.3)].

2.4.Patients with Renal Impairment: No dosage adjustment is necessary in patients with mild or moderate renal impairment. However, for patients with severe renal insufficiency, JESTAMIVAM should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. Caution should be exercised when JESTAMIVAM is administered to these patients, and they should be closely monitored [see Warnings and Precautions (5.1); Clinical Pharmacology (12.3)].

2.5.Geriatric Patients: No dosage adjustment is necessary in geriatric patients [see Clinical Pharmacology (12.3)].

2.6.Coadministration with Other Drugs: [See Warnings and Precautions (5.1) and Drug Interactions (7).]

Bile Acid Sequestrants: Dosing of JESTAMIVAM should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant [see Drug Interactions (7.4)].*Cyclosporine or Danazol:* Caution should be exercised when initiating JESTAMIVAM in the setting of cyclosporine. In patients taking cyclosporine or danazol, JESTAMIVAM should not be started unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. The dose of JESTAMIVAM should not exceed 10/10 mg/day [see Drug Interactions (7.5)].*Amiodarone or Verapamil:* In patients taking amiodarone or verapamil concomitantly with JESTAMIVAM, the dose should not exceed 10/20 mg/day [see Warnings and Precautions (5.1) and Drug Interactions (7.3)].*Other Concomitant Lipid-Lowering Therapy:*The safety and effectiveness of JESTAMIVAM administered with fibrates have not been established. Therefore, the combination of JESTAMIVAM and fibrates should be avoided [see Warnings and Precautions (5.1) and Drug Interactions (7.2 and 7.7)].There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates (especially gemfibrozil). Combination therapy with gemfibrozil should be avoided because of an increase in simvastatin exposure with concomitant use. [See Warnings and Precautions (5.1) and Drug Interactions (7.2 and 7.7).]

3.Dosage forms and strengths: JESTAMIVAM 10/40, (ezetimibe 10 mg/simvastatin 40 mg tablets)
JESTAMIVAM 10/80, (ezetimibe 10 mg/simvastatin 80 mg tablets)

4.Contraindications: Hypersensitivity to any component of this medication [see Adverse Reactions (6.2)].
Active liver disease or unexplained persistent elevations in hepatic transaminase levels [see Warnings and Precautions (5.2)].Women who are pregnant or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because HMG-CoA reductase inhibitors (statins), such as simvastatin, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, JESTAMIVAM may cause fetal harm when administered to a pregnant woman. 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 hypercholesterolemia. There are no adequate and well-controlled studies of JESTAMIVAM use during pregnancy; however, in rare reports congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, simvastatin revealed no evidence of teratogenicity. JESTAMIVAM should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, JESTAMIVAM 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 simvastatin 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 JESTAMIVAM treatment should not breast-feed their infants [see Use in Specific Populations (8.3)].

5.Warnings and precautions:*5.1 Myopathy/Rhabdomyolysis:* 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 CK >10 X the upper limit of normal (ULN) was 0.2% for (Ezetemibe& Simvastatin), 0.6% for placebo, 0.0% for ezetimibe, and 0.3% for all simvastatin doses. Simvastatin, like other statins, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above 10 X ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of statin activity in plasma. Predisposing factors for myopathy include advanced age (≥ 65 years), uncontrolled hypothyroidism, and renal impairment. As with other statins, the risk of myopathy/rhabdomyolysis is dose related. In a clinical trial database in which 41,050 patients were treated with simvastatin with 24,747 (approximately 60%) treated for at least 4 years, the incidence of myopathy was approximately 0.02%, 0.08% and 0.53% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded. 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 very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates. All patients starting therapy with JESTAMIVAM or whose dose of JESTAMIVAM is being increased should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. JESTAMIVAM therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when simvastatin treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.
Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus.
Such patients taking JESTAMIVAM merit closer monitoring. Therapy with JESTAMIVAM should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Drug Interactions: The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs that inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin,HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily). The use of JESTAMIVAM concomitantly with these CYP3A4 inhibitors should be avoided. If treatment with itraconazole,ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with JESTAMIVAM should be suspended during the course of treatment. [See Drug Interactions (7).]Diltiazem: Do not exceed 40mg simvastatin daily. The combined use of simvastatin in patients receiving diltiazem should not Exceed 40mg daily unless the clinical benefit is likely to outweight the increased risk of myopathy.The benefits of the combined use of JESTAMIVAM with the following drugs should be carefully weighed against the Potential risks of combinations: gemfibrozil, other lipid-lowering drugs (other fibrates or >1 g/day of niacin), cyclosporine, danazol, amiodarone, or verapamil .Caution should be used when prescribing other fibrates or lipid-lowering doses (≥ 1 g/day) of niacin with JESTAMIVAM, as these agents can cause myopathy when given alone. Prescribing recommendations for interacting agents are summarized in Table 1 [see also Dosage and Administration (2.6), Drug Interactions (7), and Clinical Pharmacology (11.3)].

Table 1: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis . Combination therapy with fibrates should be avoided;however, although not recommended, if JESTAMIVAM is used in combination with gemfibrozil, the dose should not exceed 10/10 mg daily.
* The benefits of the use of JESTAMIVAM in patients receiving cyclosporine or danazol should be carefully weighed against the risks of these combinations. ** The combined use of JESTAMIVAM at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Fibrates*	Avoid JESTAMIVAM
Cyclosporine* Danazol *	Do not exceed 10/10 mg JESTAMIVAM daily
Amiodarone** Verapamil**	Do not exceed 10/20 mg JESTAMIVAM daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

5.2 liver enzymes: In three placebo-controlled, 12-week trials the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.7% overall for patients treated with (Ezetimibe /Simvastatin) and appeared to be dose-related with an incidence of 2.6% for patients treated with (Ezetimibe /Simvastatin) 10/80. In controlled long-term (48week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (≥ 3 X ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with (Ezetimibe /Simvastatin) 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment.
It is recommended that liver function tests be performed before the initiation of treatment with (Ezetimibe /Simvastatin), and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 X ULN or greater persist, withdrawal of therapy with (Ezetimibe /Simvastatin) is recommended. JESTAMIVAM should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of JESTAMIVAM.

5.3.Hepatic Impairment: Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, JESTAMIVAM is not recommended in these patients. [See Clinical Pharmacology (12.3).]

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:
Vytorin: 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 practice. In the (ezetimibe/simvastatin) placebo-controlled clinical trials database of 1420 patients (age range 20-83 years, 52% women, 87% Caucasians, 3% Blacks, 5% Hispanics, 3% Asians) with a median treatment duration of 27 weeks,5% of patients on (Ezetimibe /Simvastatin) and 2.2% of patients on placebo discontinued due to adverse reactions. The most common adverse reactions in the group treated with JESTAMIVAM that led to treatment discontinuation and occurred at a rate greater than placebo were:
- Increased ALT (0.9%) ,Myalgia (0.6%) ,Increased AST (0.4%) ,Back pain (0.4%) .

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) in controlled clinical trials were: headache (5.8%), increased ALT (3.7%), myalgia (3.6%), upper respiratory tract infection (3.6%), and diarrhea (2.8%). (Ezetimibe/Simvastatin) has been evaluated for safety in more than 10,189 patients in clinical trials.Table 2 summarizes the frequency of clinical adverse reactions reported in ≥ 2% of patients treated with (Ezetimibe/Simvastatin) (n=1420) and at an incidence greater than placebo, regardless of causality assessment, from four placebo-controlled trials.

Table 2*
Clinical Adverse Reactions Occurring in ≥ 2% of Patients Treated with (Ezetimibe/Simvastatin) and at an Incidence Greater than Placebo, Regardless of Causality

Body system/organ class Adverse Reaction	Placebo (%) N=371	Ezetimibe (%) N= 302	Simvastatin** (%) N=1234	Jestamivam (Ezetimibe/Simvastatin)** (%) N= 1420
Body as a whole-general disorders				
Headache	5.4	6.0	5.9	5.8
Gastrointestinal system disorders				
Diarrhea	2.2	5.0	3.7	2.8
Infections and infestations				
Influenza	0.8	1.0	1.9	2.3
Upper respiratory tract infection	2.7	5.0	5.0	3.6
Musculoskeletal & connective tissue disorders				
Myalgia	2.4	2.3	2.6	3.6
Pain in extremity	1.3	3.0	2.0	2.3

*Includes two placebo-controlled combination studies in which the active ingredients equivalent to (Ezetimibe/Simvastatin) were coadministered and two placebo-controlled studies in which (Ezetimibe/Simvastatin) was administered. **All doses.
Ezetimibe: Other adverse reactions reported with ezetimibe in placebo-controlled studies, regardless of causality assessment: Musculoskeletal system disorders: arthralgia; Infections and infestations: sinusitis; Body as a whole – general disorders: fatigue.
Simvastatin: Other adverse reactions reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment: Cardiac disorders: atrial fibrillation; Ear and labyrinth disorders: vertigo; Gastrointestinal disorders: abdominal pain, constipation, dyspepsia, flatulence, gastritis; Skin and subcutaneous tissue disorders: eczema, rash;Endocrine disorders: diabetes mellitus; Infections and infestations: bronchitis, sinusitis, urinary tract infections; Body as a whole – general disorders: asthenia, edema/swelling; Psychiatric disorders: insomnia.
Laboratory Tests: Marked persistent increases of hepatic serum transaminases have been noted [see Warnings and Precautions (5.2)]. Elevated alkaline phosphatase and γ-glutamyl transpeptidase have been reported. About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK [see Warnings and Precautions (5.1)].

6.2 Post-Marketing Experience: Because the below 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.
The following adverse reactions have been reported in post-marketing experience for Vytorin or ezetimibe or simvastatin: pruritus; alopecia; erythema multiforme; a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails); dizziness; muscle cramps; myalgia; arthralgia; pancreatitis; memory impairment; paresthesia; peripheral neuropathy; vomiting; nausea; anemia; myopathy/rhabdomyolysis [see Warnings and Precautions (5.1)]; hepatitis/jaundice; hepatic failure; depression; cholelithiasis; cholecystitis; thrombocytopenia; elevations in liver transaminases; elevated creatine phosphokinase. Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria have been reported. In addition, an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

7.Drug interactions: [See Clinical Pharmacology (12.3).] ***7.1 CYP3A4 Interactions :***The risk of myopathy is increased by reducing the elimination of the simvastatin component of JESTAMIVAM. Hence when JESTAMIVAM is used with an inhibitor of CYP3A4 (e.g., as listed below), elevated plasma levels of HMG-CoA reductase inhibitory activity can increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of JESTAMIVAM. [See Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).] Itraconazole, ketoconazole, and other antifungal azoles,Macrolide antibiotics erythromycin, clarithromycin, and the ketolide antibiotic telithromycin ,HIV protease inhibitors ,Antidepressant nefazodone ,Grapefruit juice in large quantities (>1 quart daily) ,Concomitant use of these drugs and any medication labeled as having a strong inhibitory effect on CYP3A4 should be avoided unless the benefits of combined therapy outweigh the increased risk. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with (Ezetimibe/Simvastatin)should be suspended during the course of treatment.

7.2 Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone :The risk of myopathy is increased by gemfibrozil and to a lesser extent by other fibrates and niacin (nicotinic acid) (≥ 1 g/day) [see Warnings and Precautions (5.1)].

7.3 Amiodarone or Verapamil :The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of JESTAMIVAM [see Warnings and Precautions (5.1)].

7.4 Cholestyramine:Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding JESTAMIVAM to cholestyramine may be reduced by this interaction.

7.5 Cyclosporine or Danazol :The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of JESTAMIVAM [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].Caution should be exercised when using JESTAMIVAM and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine [see Dosage and Administration (2.6)]. Cyclosporine concentrations should be monitored in patients receiving JESTAMIVAM and cyclosporine [see Clinical Pharmacology (12.3)]. The degree of increase in ezetimibe exposure may be greater in patients with severe renal impairment. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. [See Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).]

7.6 Digoxin:In one study, concomitant administration of digoxin with simvastatin resulted in a slight elevation in plasma digoxin concentrations. Patients taking digoxin should be monitored appropriately when JESTAMIVAM is initiated.

7.7 Fibrates: The safety and effectiveness of JESTAMIVAM administered with fibrates have not been established.Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile [see Animal Toxicology and/or Pharmacology (13.2)]. Coadministration of JESTAMIVAM with fibrates is not recommended until use in patients is studied. [See Warnings and Precautions (5.1).]

7.8 Coumarin Anticoagulants : Simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in a normal volunteer study and in a hypercholesterolemic patient study, respectively. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting JESTAMIVAM and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of JESTAMIVAM is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants. Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. There have been post-marketing reports of increased INR in patients who had ezetimibe added to warfarin. Most of these
patients were also on other medications. The effect of JESTAMIVAM on the prothrombin time has not been studied.

8.use in specific populations *8.1.Pregnancy :* Pregnancy Category X. [See Contraindications (4).] JESTAMIVAM is contraindicated in women who are or may become pregnant. 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 (Ezetimibe /Simvastatin) use during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to statins in utero. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because statins, such as simvastatin, decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, JESTAMIVAM may cause fetal harm when administered to a pregnant woman. If JESTAMIVAM is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential, who require JESTAMIVAM treatment for a lipid disorder, should be advised to use effective contraception. For women trying to conceive, discontinuation of JESTAMIVAM should be considered. If pregnancy occurs, JESTAMIVAM should be immediately discontinued.***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 AUC0-24hr 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 AUC0-24hr for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.Multiple-dose studies of ezetimibe coadministered with statins in rats and rabbits during organogenesis result in Higher ezetimibe and statin exposures. Reproductive findings occur at lower doses in coadministration therapy compared to monotherapy.***Simvastatin :*** Simvastatin was not teratogenic in rats or rabbits at doses (25,10 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice. There are rare reports of congenital anomalies following intrauterine exposure to statins. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally-related statin, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

8.3 Nursing Mothers:It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants. A decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother [see Contraindications (4)]. In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed in maternal plasma. It is not known whether ezetimibe or simvastatin are excreted into human breast milk. Because a small amount of another drug in the same class as simvastatin is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women who are nursing should not take JESTAMIVAM [see Contraindications (4)].

8.4.Pediatric Use: The effects of ezetimibe coadministered with simvastatin (n=126) compared to simvastatin monotherapy (n=122) have been evaluated in adolescent boys and girls with heterozygous familial hypercholesterolemia (HeFH). In a multicenter, double-blind, controlled study followed by an open-label phase, 142 boys and 106 postmenarchal girls, 10 to 17 years of age (mean age 14.2 years, 43% females, 82% Caucasians, 4% Asian, 2% Blacks, 13% multi-racial) with HeFH were randomized to receive either ezetimibe coadministered with simvastatin or simvastatin monotherapy. Inclusion in the study required 1) a baseline LDL-C level between 160 and 400 mg/dL and 2) a medical history and clinical presentation consistent with HeFH. The mean baseline LDL-C value was 225 mg/dL (range: 161-351 mg/dL) in the ezetimibe coadministered with simvastatin group compared to 219 mg/dL (range: 149-336 mg/dL) in the simvastatin monotherapy group. The patients received coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, coadministered ezetimibe and 40 mg simvastatin or 40 mg simvastatin monotherapy for the next 27 weeks, and open-label coadministered ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter. The results of the study at Week 6 are summarized in Table 3. Results at Week 33 were consistent with those at Week 6.
Table 3: Mean Percent Difference at Week 6 Between the Pooled Ezetimibe Coadministered with Simvastatin Group and the Pooled Simvastatin Monotherapy Group in Adolescent Patients with Heterozygous Familial Hypercholesterolemia .

	Total-C	LDL-c	Apo B	Non HDL-C	TG	HDL-C
Mean percent difference Between treatment groups	-12%	-15%	-12%	-14%	-2%	+o.1%
95% Confidence Interval	(-15%, -9%)	(-18%, -12%)	(-155, -9%)	(-17%,-11%)	(-9%,+4%)	(-3%, +3%)

For triglycerides, median % change from baseline. From the start of the trial to the end of Week 33, discontinuations due to an adverse reaction occurred in 7 (6%) patients in the ezetimibe coadministered with simvastatin group and in 2 (2%) patients in the simvastatin monotherapy group. During the trial, hepatic transaminase elevations (two consecutive measurements for ALT and/or AST >3 X ULN) occurred in four (3%) individuals in the ezetimibe coadministered with simvastatin group and in two (2%) individuals in the simvastatin monotherapy group. Elevations of CPK (≥10 X ULN) occurred in two (2%) individuals in the ezetimibe coadministered with simvastatin group and in zero individuals in the simvastatin monotherapy group. In this limited controlled study, there was no significant effect on growth or sexual maturation in the adolescent boys or girls, or on menstrual cycle length in girls. Coadministration of ezetimibe with simvastatin at doses greater than 40 mg/day has not been studied in adolescents. Also, (Ezetimibe /Simvastatin) has not been studied in patients younger than 10 years of age or in premenarchal girls. ***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.
Simvastatin: The pharmacokinetics of simvastatin has not been studied in the pediatric population.***8.5.Geriatric Use:*** Of the 10,189 patients who received (Ezetimibe/Simvastatin) in clinical studies, 3242 (32%) were 65 and older (this included 844 (8%) who were 75 and older). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients but greater sensitivity of some older individuals cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, JESTAMIVAM should be prescribed with caution in the elderly. [See Clinical Pharmacology (11.3).] ***8.6 Renal Impairment:*** Caution should be exercised when JESTAMIVAM is administered to patients with severe renal impairment.[See Dosage and Administration (2.4).]***8.7 Hepatic Impairment:*** JESTAMIVAM is contraindicated in patients with active liver disease or unexplained persistent elevations of hepatic transaminases. JESTAMIVAM is not recommended in patients with moderate to severe hepatic impairment. [See Contraindications (4) and Warnings and Precautions (5.2).]

9.Overdosage: No specific treatment of overdosage with JESTAMIVAM can be recommended. In the event of an Overdose, symptomatic and supportive measures should be employed. ***Ezetimibe:***In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hyperlipidemia for up to 56 days was generally well tolerated. A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. ***Simvastatin:***Significant lethality was observed in mice after a single oral dose of 9 g/m^2 No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2 respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools. A few cases of overdosage with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. The dialyzability of simvastatin and its metabolites in man is not known at present.

10. Description: JESTAMIVAM contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, an 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 C24H21F2NO3 and 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.Simvastatin, an inactive lactone, is hydrolyzed to the corresponding ß-hydrxyacid form, which is an inhibitor of HMG-CoA reductase. Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S[1α,3α,7β,8β(2S*,4S*),-8aβ]]. The empirical formula of simvastatin is C 25H38O5 and its molecular weight is 418.57. Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water and freely soluble in chloroform, methanol and ethanol. Jestamivam is available for oral use as tablets containing 10 mg of Ezetimibe & 40 mg of simivastatin(Jestamivam 10/40),or 80 mg of simvastatin(Jestamivam 10/80) each tablet contains the following inactive ingredrents:Microcrystalline cellulose,butylated hydroxyanisole,citric acid,croscarmellose sodium,hypromellose,lactose monohydrate,magnesium searate and propyl gallate.

11.Clinical pharmacology: *11.1 Mechanism of Action:* Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. JESTAMIVAM contains ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. JESTAMIVAM reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.
Ezetimibe:Ezetimibe 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 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)].
Simvastatin :Simvastatin is a prodrug and is hydrolyzed to its active ß-hydrxyacid form, simvastatin acid, after administration. Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces very-low-density lipoproteins (VLDL) and TG and increases HDL-C.

11.2 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 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.

11.3 Pharmacokinetics: The results of a bioequivalence study in healthy subjects demonstrated that the (ezetimibe/simvastatin)10 mg/10 mg to 10 mg/80 mg combination tablets are bioequivalent to coadministration of corresponding doses of ezetimibe (ZETIA®) and simvastatin (ZOCOR®) as individual tablets.
Absorption: Ezetimibe: After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Simvastatin:The availability of the ß-hydrxyacid to the systemic circulation following an oral dose of simvastatin was found to be less than 5% of the dose, consistent with extensive hepatic first-pass extraction.
Effect of Food on Oral Absorption: Ezetimibe:Concomitant food administration (high-fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as 10-mg tablets. The Cmax value of ezetimibe was increased by 38% with consumption of high-fat meals.Simvastatin: Relative to the fasting state, the plasma profiles of both active and total inhibitors of HMG-CoA reductase were not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.
Distribution: Ezetimibe:Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins. Simvastatin: Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. When radiolabeled simvastatin was administered to rats, simvastatin-derived radioactivity crossed the blood-brain barrier.
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 14C-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.Simvastatin:Simvastatin is a lactone that is readily hydrolyzed in vivo to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is a basis for an assay in pharmacokinetic studies of the ß-hydrxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives.Following an oral dose of 14C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. Plasma concentrations of total radioactivity (simvastatin plus 14C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose.
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.Simvastatin: In a study including 16 elderly patients between 70 and 78 years of age who received simvastatin 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45%

compared with 18 patients between 18-30 years of age. **Pediatric Patients:** [See Pediatric Use (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.**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 was similar to those seen in Caucasian subjects. **Hepatic Impairment :** Ezetimibe: After a single10-mg dose of ezetimibe, the mean exposure (based on area under the curve [AUC]) to 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 compared to healthy subjects. **Renal Impairment:** Ezetimibe: After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m^2), the mean AUC for total ezetimibe and ezetimibe increased approximately 1.5-fold, compared to healthy subjects (n=9). Simvastatin :Pharmacokinetic studies with another statin having a similar principal route of elimination to that of simvastatin have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal impairment (as measured by creatinine clearance).***Drug Interactions*** [See also Drug Interactions (7).] :No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin. No specific pharmacokinetic drug interaction studies with Vytorin ((Ezetimibe /Simvastatin)have been conducted other than the following study with NIASPAN (Niacin extended-release tablets).
Niacin: The effect of (Ezetimibe/Simvastatin) (10/20 mg daily for 7 days) on the pharmacokinetics of NIASPAN extended-release tablets (1000 mg for 2 days and 2000 mg for 5 days following a low-fat breakfast) was studied in healthy subjects. The mean Cmax and AUC of niacin increased 9% and 22%, respectively. The mean Cmax and AUC of nicotinuric acid increased 10% and 19%, respectively (N=13). In the same study, the effect of NIASPAN on the pharmacokinetics of (Ezetimibe/Simvastatin) was evaluated (N=15). While concomitant NIASPAN decreased the mean Cmax of total ezetimibe (1%), and simvastatin (2%), it increased the mean Cmax of simvastatin acid (18%). In addition, concomitant NIASPAN increased the mean AUC of total ezetimibe (26%), simvastatin (20%), and simvastatin acid (35%).
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. In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This indicates that simvastatin is not an inhibitor of CYP3A4 and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4. Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of statins. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4. Simvastatin is a substrate for CYP3A4. Inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy. [See Warnings and Precautions (5.1); Drug Interactions (7.1).] **Table 4 Effect of coadministered drugs on total Ezetimibe .**

Coadministerd drug and dosing regimen	Total Ezetimibe*	
	Change in AUC	Change in C max
Cyclosporine-stable dose required (75-150 mg BID) **	↑240 %	↑290 %
Fenofibrate,200mg QD,14days[1]	↑48 %	↑64 %
Gemifibrozil,600mg BID,7days[1]	↑64 %	↑91 %
Cholestyramine,4g BID,14 days[1]	↓55 %	↓4 %
Aluminum & magnesium hydroxide combination antacid, single dose[2]	↓4 %	↓30 %
Cimetidine,400mg BID,7 days	↑6 %	↑22 %
Glipizide,10mg,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 diffrent study,a renal transplant patient with severe renal insuffuciency (creatinine clearance of 13.2 ml/min/ 1.73 m^2) who was recieving multiple medications,including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to healthy subjects.
1-See 7.Drug interactions.
2-Supralox 20ml

Table 5 Effectof ezetimibe coadministration on systematic exposure to other drugs.

Co-administered drug and its dosage regimen	Ezetimibe dosage regimen	Change in AUC of Co-administered drug	Change in C_{max} of Co-administered 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,0.5mg single dose	10 mg QD,8 days	↑2%	↓7%
Gemifibrozil,600mg BID,7Days[1]	10 mg QD,7 days	↓1%	↓11%
Ethinyl estradiol & Levonorgestrel,QD,21 days	10 mg QD,Days8 to 14 or 21 day oral contraceptive cycle	0%(Ethinyl estradiol) 0%(Levonorgestrel)	↓9%(Ethinyl estradiol) ↓5%(Levonorgestrel)
Glipizide,10 mg on day 1 and 9	10 mg QD,2-9 days	↓3%	↓5%
Fenofibrate,200mg QD,14 days[1]	10 mg QD,14 days	↑11%	↑7%
Cyclosporine,100mg 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] See7.Drug interactions			

Table 6 Effect of coadministered drugs or grapefruit juice on simvastatin systematic exposure.

Co-administered drug or grape fruit juice	Dosing of co-administered drug or grapefruit juice	Dosing of simvastatin	Geometric mean ratio (Ratio with /without co-administered drug) No effect =1.00		
				AUC	C_{max}
Avoid taking with jestamivam (see Warning s and Precautions{5:1})					
Telithromycin*	200 mg QD,4 days	80 mg	Simvastatin acid« Simvastatin	12 8.9	15 5.3
Nelfinavir	1250 mg BID for 14 days	20 mg QD for 28 days	Simvastatin acid« Simvastatin	6	6.2
Itraconazole*	200 mg QD,4 days	80 mg	Simvastatin acid« Simvastatin		13.1 13.1
Avoid > 1 quart of grapefruit juice with jestamivam (see Warnings and Precautions{5:1})					
Grape fruit juice∞ (high dose)	200 ml of double-strength TID ¶	60 mg single dose	Simvastatin acid« Simvastatin	7 16	
Grape fruit juice∞ (Low dose)	8 oz (about 237 ml) of single-strength#	20 mg single dose	Simvastatin acid« Simvastatin	1.3 1.9	
Avoid taking with jestamivam.if jestamivam is used in combination with gemifebrozil, the dose should not exceed 10/10 mg daily, based on clinical and/or post-marketing simvastatin experience (see Warnings and Precautions{5:1})					
Gemifibrozil	600 mg BID for 3 days	40 mg	Simvastatin acid« Simvastatin	2.85 1.35	2.18 0.91
Avoid taking with >10/20 jestamivam, based on clinical and/or post-marketing simvastatin experience(see Warnings and Precautions{5:1})					
Verapamil SR	240 mg QD days 1-7 then 240 mg BID on days 8-10	80 mg on day 10	Simvastatin acid Simvastatin	2.3 2.5	2.4 2.1
No dosing adjustments required for the following:					
Fenofibrate	160 mg QDx14 days	80 mg QD on days 8-14	Simvastatin acid Simvastatin	0.64 0.89	0.89 0.83
Diltiazem	120 mg BID for 10 days	80 mg on day 10	Simvastatin acid Simvastatin	2.69 3.1	2.69 2.88
Amlodipine	10 mg QDx10 days	80 mg on day 10	Simvastatin acid Simvastatin	1.58 1.77	1.56 1.47
Propanolol	80 mg single dose	80 mg single dose	Total inhibitor Active inhibitor	0.79 0.79	↓ from 33.6 to 21.1 ng.eq/ml ↓ from 7.0 to 4.7 ng.eg/ml

- Results based on a chemical assay except results with propranolol as indicated.* Results could be representative of the following CYP 3A4 inhibitors: Ketoconazole,erythromycin,clarithromycin,HIV protease inhibitors,and nefazodone.

«Simvastatin acid refers to ß-hydrxyacid of simvastatin.∞The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.¶Double-strenght: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 ml together with single dose simvastatin and 30 and 90 minutes following single dose simvastatin on day 3.# Single-strenght : one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days. And simvastatin was administered in the evening on day 3.

12. nonclinical toxicology :*12.1.Carcinogenesis, Mutagenesis, Impairment of Fertility:* No animal carcinogenicity or fertility studies have been conducted with the combination of ezetimibe and simvastatin. The combination of ezetimibe with simvastatin 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 simvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin (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 AUC0-24hr 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 AUC0-24hr 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 AUC0-24hr for total ezetimibe). Simvastatin: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively, (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).
In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC). A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80-mg daily dose. No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an in vitro alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an in vitro chromosome aberration study in CHO cells, or an in vivo chromosomal aberration assay in mouse bone marrow. There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m 2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day (approximately2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear. ***12.2 Animal Toxicology and/or Pharmacology:*** CNS Toxicity: Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day. A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose. CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class. There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).Ezetimibe:The hypocholesterolemic effect of ezetimibe was evaluated in cholesterol-fed Rhesus monkeys, dogs, rats, and mouse models of human cholesterol metabolism. Ezetimibe was found to have an ED50 value of 0.5 µg/kg/day for inhibiting the rise in plasma cholesterol levels in monkeys. The ED50 values in dogs, rats, and mice were 7, 30, and 700 µg/kg/day, respectively. These results are consistent with ezetimibe being a potent cholesterol absorption inhibitor.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 14C-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. **13 Clinical studies:*13.1 Primary Hyperlipidemia:*** Vytorin:Vytorin reduces total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C in patients with hyperlipidemia. Maximal to near maximal response is generally achieved within 2 weeks and maintained during chronic therapy. Vytorin 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 Vytorin.Five multicenter, double-blind studies conducted with either Vytorin or coadministered ezetimibe and simvastatin equivalent to Vytorin in patients

چستاميڤام

إزيتيميب/ سيمفاستاتين

أقراص

بيان التركيب: چستاميڤام ٤٠/١٠ **المواد الفعالة:**إزتيمايب ١٠مجم ، سيمفاستاتين ٤٠مجم.
چستاميڤام ٨٠/١٠ **المواد الفعالة:**إزتيمايب ١٠مجم، سيمفاستاتين ٨٠مجم.
المواد الغير فعالة: مايكروكريستالاين سيليلوز ،بيتايلاتد هيدروكسيانيزول، حمض الستريك ، كروسكرميلوز صوديوم، هيبروميلوز، لاكتوز مونوهايدرات ، ستيرات الماغنيسيوم، ، بروبايل جالات.

١- ماهو چستاميڤام وماهو استخدامه؟ : چستاميڤام يحتوى علي إيزتيمايب و سيمفاستاتين مادتين مخفضتين للكوليسترول. چيستاميڤام يقلل الكوليسترول المرتفع، و الدهون الثلاثية و الكوليسترول النوعى الضار. وأيضا يرفع مستوى الكوليسترول النوعى المفيد. چيستاميڤام للمرضى الغير قادرين على ضبط الكوليسترول بتنظيم الطعام او ممارسة الرياضة فقط. يجب الإستمرار على نظام غذائى منخفض الكوليسترول أثناء إستخدام الدواء.
چيستاميڤام يقلل الكوليسترول عن طريق تقليل إمتصاص الكوليسترول عن طريق الجهاز الهضمى وأيضا تقليل الكوليسترول المصنع فى الجسم نفسه.
چيستاميڤام لا يساعد على تقليل الوزن. چيستاميڤام لا يقلل من النوبات القلبية أو السكتة الدماغية اكثر من سيمفاستاتين منفرداً.

٢- من لا يتناول چيستاميڤام: لا تتناول چيستاميڤام:• الحساسية للإزتيمايب أو سيمفاستاتين أوأى من مكونات المستحضر.• في حالة وجود أمراض بالكبد أو التحاليل المتكررة للدم تظهر إمكانية أمراض الكبد.• في حالة الحمل او الرضاعة الطبيعية.• في حالة السيدات في سن الإنجاب يجب إستخدام وسيلة منع الحمل أثناء إستخدام چيستاميڤام. لا توجد دراسات للأطفال أقل من ١٠ سنوات.

ما يجب ابلاغه للطبيب قبل و أثناء تناول چيستاميڤام:أبلغ الطبيب فى حالة وجود آلم بالعضلات غير مبرر، إيلام أو وهن. وذلك بسبب في حالات نادرة، مشاكل العضلات يمكن أن تكون خطيرة وتشمل إنهيار العضلات مما يؤدى إلى تلف الكلى.خطر حدوث إنهيار العضلات هو أكبر في الجرعات العالية من چيستاميڤام.تناول چيستاميڤام مع بعض المواد يمكن أن يزيد من خطر مشاكل العضلات. يجب إبلاغ الطبيب فى حالة تناول أى من الأتى:
• دلتيازيم (جرعة السيمفاستاتين لا تتعدى ٤٠ مجم يومياً).• سيكلوسبورين.• دانازول.• مضادات الفطريات (مثل إيتراكونازول أو كيتوكونازول).• مشتقات حمض الفبريك (مثل جيمفبروزيل، بزافايبرات أو فينوفايبرات).• المضادات الحيوية إريثرومايسين ، كلاريثرومايسن و تليثرومايسن.
• أدوية فيروس نقص المناعة البشرية مثل اندينافير، نلفينافير، ريتونافير و ساكوينافير.• مضاد الإكتئاب نفازادون.• أميودارون (لعلاج عدم انتظام ضربات القلب).• فيراباميل (المستخدم لعلاج ضغط الدم المرتفع، آلم الصدر المصاحب للأمراض القلبية أو الأمراض القلبية الاخرى)• الجرعات العالية (≥ ١ جرام/يوميا) من نياسين أو حمض النيكوتينيك.• كميات كبيرة من عصير جريب فروت (> ١كوارت يومياً).من المهم أيضا إبلاغ الطبيب في حالة تناول كومارين مضادات التجلط (أدوية لمنع تجلط الدم مثل وارفارين).أبلغ الطبيب عن أى دواء تتناوله ويشمل أيضا الأعشاب الطبية.أبلغ الطبيب عن أى مشاكل صحية و تشمل الحساسية.

أبلغ الطبيب فى حالة: • تناول كميات كبيرة من الكحوليات أو وجود مشاكل فى الكبد. چيستاميڤام قد لا يكون مناسب.• الحمل لا تستخدم چيستاميڤام. إذا حدث حمل أثناء إستخدام چيستاميڤام أوقفه فوراً و أبلغ الطبيب.• الرضاعة الطبيعية لا تستخدم چيستاميڤام.أبلغ الأطباء الأخرين بتناولك چيستاميڤام.

٣- كيفية تناول چستاميڤام:الطبيب يصف الجرعة المناسبة من چيستاميڤام. الجرعات المتوفرة من چيستاميڤام هى (٤٠/١٠ و ٨٠/١٠).
الجرعة تبدأ عادة بچيستاميڤام٢٠/١٠.• يؤخذ الدواء مرة واحدة ، مساءً، مع أو بدون طعام.• يؤخذ چيستاميڤام كما هو موصوف من الطبيب. فى حالة نسيان جرعة لا تتناول جرعة أكبر.• إستمر فى نظام غذائى منخفض الكوليسترول أثناء تناول چيستاميڤام. إستشر الطبيب عن أى معلومات عن النظام الغذائى.• إستمر فى تناول چيستاميڤام حتى يطلب الطبيب إيقاف الدواء. إذا أوقفت تناول چيستاميڤام يمكن أن ترتفع نسبة الكوليسترول.

في حالة تناول جرعة أكبر من المحدد:• يجب إبلاغ الطبيب فوراً.

الأثار الجانبية: تابع مع الطبيب بصورة منتظمة لمتابعة نسبة الكوليسترول و متابعة الأثار الجانبية. يمكن للطبيب عمل تحليل دم لمتابعة الكبد قبل البدء فى إستخدام چيستاميڤام أو أثناء العلاج.مثل جميع الأدوية يمكن حدوث بعض الأثار الجانبية مع چستاميڤام.
الأثار الجانبية المالوفة أثناء تناول چيستاميڤام : صداع ، الم بالعضلات، إسهال.الأثار الجانبية التالية ظهرت مع (إزتيمايب/ سيمفاستاتين) أو مع إزتيمايب أوسيمفاستاتين أقراص.- حساسية و تشمل تورم الوجه، الشفتين ، اللسان و/أو الحلق مما يؤدى إلى صعوبة فى التنفس أو البلع، طفح جلدى، أرتكاريا، آثار طفح أحمر، ألم بالمفاصل، آلم بالعضلات، تغير فى بعض تحليلات الدم، مشاكل بالكبد (أحيانا خطيرة)، إلتهاب البنكرياس، غثيان، دوخة، نخز، إكتئاب، حصوات صفراوية، إلتهابا بالمرارة، إضطراب النوم ، مشاكل فى الذاكرة. برجاء إبلاغ الطبيب فى حالة ظهور الأعراض الجانبية أو ظهور آثار أخرى غير مدرجة.

ما يجب معرفته عن إرتفاع الكوليسترول:الكوليسترول نوع من أنواع الدهون الموجودة بالدم. الكولسترول له مصدران. من الجسم أو من الطعام. الكوليسترول الكلى يتكون من الكوليسترول النوعى الضار و الكوليسترول النوعى المفيد.الكوليسترول النوعي الضار يسمى بذلك لامكانية ترسبها على جدار الشرايين مما يؤدى إلى ضيق بالشرايين. هذا الضيق يمكن أن يؤدى إلى قلة أو عدم وصول الدم إلى القلب، المخ أو الأعضاء الأخرى. إرتفاع الكوليسترول النوعى الضار هو من الأسباب الرئيسية لأمراض القلب و أحد أسباب السكتة الدماغية.الكوليسترول النوعى المفيد يمنع ترسيب الكوليسترول النوعى الضار على الشرايين.الدهون الثلاثية- نوع من أنواع الدهون الموجودة بالجسم.

معلومات عامة حول چيستاميڤام :يمكن وصف العلاج أحيانا فى حالات غير مدرجة فى هذه النشرة. لا تستخدم چيستاميڤام فى حالة غير الموصوفة من الطبيب. لا توصف چيستاميڤام لأخرين حتى إذا كانوا يعانوا من نفس الأعراض.

العبوة وظروف التخزين : يحفظ بعيداً عن متناول الأطفال.
يحفظ في درجة حرارة لا تتعدى ٣٠ درجة مئوية في مكان جاف.
چستاميڤام٤٠/١٠:عبوة كرتون بها شريط أو شريطين أو ثلاثة شرائط (الو/بي في سي) بكل منهما ١٠ أقراص مغلفة ونشرة مرفقة.
چستاميڤام٨٠/١٠:عبوة كرتون بها شريط أو شريطين أو ثلاثة شرائط (الو/بي في سي) بكل منهما ١٠ أقراص مغلفة ونشرة مرفقة.

إنتاج:

المجموعة المصرية للصناعات الدوائية-مصر.

with primary hyperlipidemia are reported:two were comparisons with simvastatin, two were comparisons with atorvastatin, and one was a comparison with rosuvastatin.In a multicenter, double-blind, placebo-controlled, 12-week trial, 1528 hyperlipidemic patients were randomized to one of ten treatment groups: placebo, ezetimibe (10 mg), simvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or Vytorin (Ezetimibe/Simvastatin) (10/10, 10/20, 10/40, or 10/80). When patients receiving Vytorin were compared to those receiving all doses of simvastatin, Vytorin significantly lowered total-C, LDL-C, Apo B, TG, and non-HDL-C. The effects of Vytorin on HDL-C were similar to the effects seen with simvastatin. Further analysis showed Vytorin significantly increased HDL-C compared with placebo. (See Table 7.) The lipid response to Vytorin was similar in patients with TG levels greater than or less than 200 mg/dL. Table 7: **Response to Vytorin in Patients with Primary Hyperlipidemia (Mean a % Change from Untreated Baseline)b**

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG a	Non-HDL-C
Pooled Data (All Ezetim Simvastatin doses)c	609	-38	-53	-42	+7	-24	-49
Pooled Data (All Simvastatin doses)c	622	-28	-39	-32	+7	-21	-36
Ezetimibe 10mg	149	-13	-19	-15	+5	-11	-18
Placebo	148	-1	-2	0	0	-2	-2
Vytorin by dose							
10/10	152	-31	-45	-35	+8	-23	-41
10/20	156	-36	-52	-41	+10	-24	-47
10/40	147	-39	-55	-44	+6	-23	-51
10/80	154	-43	-60	-49	+6	-31	-56
Simvastatin by dose							
10mg	158	-23	-33	-26	+5	-17	-30
20mg	150	-24	-34	-28	+7	-18	-32
40mg	156	-29	-41	-33	+8	-21	-38
80mg	158	-35	-49	-39	+7	-27	-45

a For triglycerides,median% change from baseline
b Baseline-on no lipid-lowering drug
c Vytorin doses pooled(10/10-10/80) significantly reduced total-C, LDL-c, ApoB,TG and non-HDL-C compared to simvastatin and significantly increased HDL-C compared to placebo.
In a multicenter, double-blind, controlled, 23-week study, 710 patients with known CHD or CHD risk equivalents, as defined by the NCEP ATP III guidelines, and an LDL-C ≥130 mg/dL were randomized to one of four treatment groups: coadministered ezetimibe and simvastatin equivalent to Vytorin (10/10, 10/20, and 10/40)or simvastatin 20 mg. Patients not reaching an LDL-C <100 mg/dL had their simvastatin dose titrated at 6-week intervals to a maximal dose of 80 mg. At Week 5, the LDL-C reductions with Vytorin 10/10, 10/20, or 10/40 were significantly larger than with simvastatin 20 mg (see Table 8).

Table (8): Response to Vytorin after 5 weeks in Patients with CHD or CDH Risk Equivalents And an LDL-C ≥ 130mg/dl.

	Simvastatin 20mg	Vytorin 10/10	Vytorin 10/20	Vytorin 10/40
N	253	251	109	97
Mean baseline LDL-C	174	165	167	171
Percent change LDL-C	-38	-47	-53	-59

In a multicenter, double-blind, 6-week study, 1902 patients with primary hyperlipidemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of eight treatment groups Vytorin(10/10, 10/20, 10/40, or 10/80) or atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg). Across the dosage range, when patients receiving Vytorin were compared to those receiving milligram-equivalent statin doses of atorvastatin, Vytorin lowered total-C, LDL-C, Apo B, and non-HDL-C significantly more than atorvastatin. Only the 10/40 mg and 10/80 mg Vytorin doses increased HDL-C significantly more than the corresponding milligram-equivalent statin dose of atorvastatin. The effects of Vytorin on TG were similar to the effects seen with atorvastatin. (See Table 9.)

Table 9 :Response to Vytorin and Atorvastatin in Patients with Primary Hyperlipidemia(mean a % change from untreated baseline)b

Treatment (Daily Dose)	N	Total-C(c)	LDL-C (c)	Apo B (c)	HDL-C	TG a	Non-HDL-C(c)
Vytorin by dose							
10/10	230	-34(d)	-47(d)	-37(d)	+8	-26	-43(d)
10/20	233	-37(d)	-51(d)	-40(d)	+7	-25	-46(d)
10/40	236	-41(d)	-57(d)	-46(d)	+9(d)	-27	-52(d)
10/80	224	-43(d)	-59(d)	-48(d)	+8(d)	-31	-54(d)
Atorvastatin by dose							
10mg	235	-27	-36	-31	+7	-21	-34
20mg	230	-32	-44	-37	+5	-25	-41
40mg	232	-36	-48	-40	+4	-24	-45
80mg	230	-40	-53	-44	+1	-32	-50

a For triglycerides,median% change from baseline
b Baseline-on no lipid-lowering drug
c Vytorin doses pooled(10/10-10/80) significantly reduced total-C, LDL-c, ApoB,TG and non-HDL-C compared to atorvastatin doses pooled(10-80)
d p<0.05 for difference with atorvastatin at equal mg doses of simvastatin component.In a multicenter, double-blind, 24-week, forced-titration study, 788 patients with primary hyperlipidemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to receive coadministered ezetimibe and simvastatin equivalent to Vytorin (10/10 and 10/20) or atorvastatin 10 mg. For all three treatment groups, the dose of the statin was titrated at 6-week intervals to 80 mg. At each pre-specified dose comparison, Vytorin lowered LDL-C to a greater degree than atorvastatin (see Table 10).

Table 10:Response to Vytorin and Atorvastatin in Patients with Primary Hyperlipidemia (Mean a % Change from Untreated Baseline) b

Treatment	N	Total-C	LDL-C	Apo B	HDL-C	TG a	Non-HDL-C
Week 6							
Atorvastatin 10mg (c)	262	-28	-37	-32	+5	-23	-35
Vytorin 10/10(d)	263	-34(f)	-46(f)	-38(f)	+8(f)	-26	-43(f)
Vytorin 10/20(e)	263	-37(f)	-50(f)	-41(f)	+10(f)	-25	-46(f)
Week 12							
Atorvastatin 20mg	246	-33	-44	-38	+7	-28	-42
Vytorin 10/20	250	-37(f)	-50(f)	-41(f)	+9	-28	-46(f)
Vytorin 10/40	252	-39(f)	-54(f)	-45(f)	+12(f)	-31	-50(f)
Week 18							
Atorvastatin 40mg	237	-37	-49	-42	+8	-31	-47
Vytorin 10/40(g)	482	-40(f)	-56(f)	-45(f)	+11(f)	-32	-52(f)
Week 24							
Atorvastatin 80mg	228	-40	-53	-45	+6	-35	-50
Vytorin 10/80(g)	459	-43(f)	-59(f)	-49(f)	+12(f)	-35	-55(f)

a For triglycerides,median% change from baseline
b Baseline-on no lipid-lowering drug
c Atorvastatin:10mg start dose titrated to 20mg,40mg and 80mg through weeks 6, 12, 18 and 24.
d Vytorin: 10/10 start dose titrated to 10/20mg,10/40mg and10/ 80mg through weeks 6, 12, 18 and 24.
E Vytorin: 10/20 start dose titrated to 10/40mg,10/40mg and 10/ 80mg through weeks 6, 12, 18 and 24.
f p<0.05 for difference with atorvastatin in the specific week.
g Data pooled for common doses of(Ezetemibe/Simvastatin) at weeks 18 and 24.
In a multicenter, double-blind, 6-week study, 2959 patients with primary hyperlipidemia, who had not met their NCEP ATP III target LDL-C goal, were randomized to one of six treatment groups: Vytorin10/20, 10/40, or 10/80) or rosuvastatin (10 mg, 20 mg, or 40 mg).The effects of Vytorin (Ezetemibe/Simvastatin) and rosuvastatin on total-C, LDL-C, Apo B, TG, non-HDL-C and HDL-C are shown in Table 11.

Response to Vytorin (Ezetimibe/Simvastatin) and Rosuvastatin in Patients with Primary Hyperlipidemia (Mean a % Change from Untreated Baseline) b

Treatment (Daily Dose)	N	Total-C(c)	LDL-C (c)	Apo B (c)	HDL-C	TG a	Non-HDL-C(c)
Vytorin by dose							
10/20	476	-37(d)	-52(d)	-42(d)	+7	-23	-47(d)
10/40	477	-39(e)	-55(e)	-44(e)	+8	-27	-50(e)
10/80	474	-44(f)	-61(f)	-50(f)	+8	-30(f)	-56(f)
Rosuvastatin by dose							
10mg	475	-32	-46	-37	+7	-20	-42
20mg	478	-37	-52	-43	+8	-26	-48
40mg	475	-41	-57	-47	+8	-28	-52

a For triglycerides,median% change from baseline
b Baseline-on no lipid-lowering drug
c Vytorin doses pooled(10/20-10/80) significantly reduced total-C,LDL-c, ApoB,TG and non-HDL-C compared to rosuvastatin doses pooled(10-40)
d p<0.05 vs rosuvastatin 10mg
e p<0.05 vs rosuvastatin 20mg
f p<0.05 vs rosuvastatin 40mg
In a multicenter, double-blind, 24-week trial, 214 patients with type 2 diabetes mellitus treated with thiazolidinediones (rosiglitazone or pioglitazone) for a minimum of 3 months and simvastatin 20 mg for a minimum of 6 weeks were randomized to receive either simvastatin 40 mg or the coadministered active ingredients equivalent to Vytorin 10/20. The median LDL-C and HbA1c levels at baseline were 89 mg/dL and 7.1%, respectively. Vytorin 10/20 was significantly more effective than doubling the dose of simvastatin to 40 mg. The median percent changes from baseline for Vytorin vs. simvastatin were: LDL-C -25% and -5%; total-C -16% and -5%; Apo B -19% and -5%; and non-HDL-C -23% and -5%. Results for HDL-C and TG between the two treatment groups were not significantly different.Ezetimibe:In two multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hyperlipidemia, ezetimibe significantly lowered total-C (-13%), LDL-C (-19%), Apo B (-14%), and TG (-8%), and increased HDL-C (+3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, and baseline LDL-C. Simvastatin: In two large, placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (N=4,444 patients) and the Heart Protection Study (N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths; the risk of non-fatal myocardial infarction and stroke; and the need for coronary and non-coronary revascularization procedures. No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.***13.2 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=14) receiving simvastatin 40 mg at baseline. Increasing the dose of simvastatin from 40 to 80 mg (n=5) produced a reduction of LDL-C of 13% from baseline on simvastatin 40 mg. Coadministered ezetimibe and simvastatin equivalent to Vytorin (10/40 and 10/80 pooled, n=9), produced a reduction of LDL-C of 23% from baseline on simvastatin 40 mg. In those patients coadministered ezetimibe and simvastatin equivalent to Vytorin(10/80, n=5), a reduction of LDL-C of 29% from baseline on simvastatin 40 mg was produced.

14.How supplied/storage and handling:
Jestamivam 10/40: Carton box containing 1,2 or 3(Al/PVC) strips, each one of 10 tablets & an inner leaflet.
Jestamivam 10/80: Carton box containing 1,2 or 3(Al/PVC) strips, each one of 10 tablets & an inner leaflet.
Storage: Storage temperature not exceeding 30°C in a dry place.

15.Patient counseling 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. Patients should be advised about substances they should not take concomitantly with JESTAMIVAM [see Warnings and Precautions (5.1)]. Patients should also be advised to inform other physicians prescribing a new medication that they are taking JESTAMIVAM.
15.1 Muscle Pain:All patients starting therapy with JESTAMIVAM should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities of grapefruit juice. They should discuss all medication, both prescription and over the counter, with their healthcare professional. ***15.2 Liver Enzymes:***It is recommended that liver function tests be performed before the initiation of JESTAMIVAM, and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (e.g., semiannually) for the first year of treatment.***15.3 Pregnancy:*** Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using JESTAMIVAM. Discuss future pregnancy plans with your patients, and discuss when to stop taking JESTAMIVAM if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking JESTAMIVAM and call their healthcare professional.
15.4 Breast-feeding: Women who are breast-feeding should be advised to not use JESTAMIVAM. Patients who have a lipid disorder and are breast-feeding should be advised to discuss the options with their healthcare professional.JESTAMIVAM is available for oral use as tablets containing 10 mg of ezetimibe, and 40 mg of simvastatin (JESTAMIVAM 10/40), or 80 mg of simvastatin (JESTAMIVAM 10/80). ***Each tablet contains the following inactive ingredients:*** Microcrystalline cellulose, butylated hydroxyanisole , citric acid, , croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate and propyl gallate. • Data presented in this insert leaflet are cited from that of the innovator (Vytorin)

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