HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JUVISYNC safely and effectively. See full prescribing information for JUVISYNC.

JUVISYNC™ (sitagliptin and simvastatin) Tablets
Initial U.S. Approval: 2011

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

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

JUVISYNC (sitagliptin and simvastatin) is indicated in patients for whom treatment with both sitagliptin and simvastatin is appropriate. (1)

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1)

Simvastatin is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events. (1.2)
- Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. (1.2)
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbeta-lipoproteinemia. (1.2)
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia. (1.2)

Important Limitations of Use:

- JUVISYNC should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. (1.3)
- JUVISYNC has not been studied in patients with a history of pancreatitis. (1.3, 5.1)
- JUVISYNC has not been studied in Fredrickson types I and V dyslipidemias. (1.3)
- Patients with severe renal impairment who require sitagliptin 25 mg should not use JUVISYNC due to the unavailability of this dosage strength for JUVISYNC. (1.3)

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

- Doses are 100 mg/10 mg, 100 mg/20 mg, 100 mg/40 mg, 50 mg/10 mg, 50 mg/20 mg, and 50 mg/40 mg per day. (2.1)
- Recommended usual starting dose for patients with normal or mildly impaired renal function is 100 mg/40 mg once a day in the evening. (2.1)
- Adjustment of the starting dose to 50 mg/40 mg once a day is recommended for patients with moderate renal impairment (CrCl greater than or equal to 30 to less than 50 mL/min, equivalent to serum Cr levels greater than 1.7 to less than or equal to 3.0 mg/dL for men and greater than 1.5 to less than or equal to 2.5 mg/dL for women). (2.2)
- Patients already taking simvastatin (10, 20, or 40 mg) can initiate JUVISYNC at a dose of 100 or 50 mg sitagliptin and the dose of simvastatin already being taken. (2.1)

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

Tablets (sitagliptin/simvastatin): 100 mg/10 mg, 100 mg/20 mg, 100 mg/40 mg, 50 mg/10 mg, 50 mg/20 mg, and 50 mg/40 mg (3)

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

- History of a serious hypersensitivity reaction, such as anaphylaxis or angioedema, to any component of this medication. (4, 5.6, 6.2)
- Concomitant administration of strong CYP3A4 inhibitors. (4, 5.2)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol. (4, 5.2)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. (4, 5.3)
- Women who are pregnant or may become pregnant. (4, 8.1)
- Nursing mothers. (4, 8.3)

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

- There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue JUVISYNC. (5.1)
- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥65), female gender, uncontrolled hypothyroidism, and renal impairment. (4, 5.2, 8.5)
- Patients should be advised to report promptly any unexplained and/or persistent muscle pain, tenderness, or weakness. JUVISYNC therapy should be discontinued immediately if myopathy is diagnosed or suspected. See Drug Interaction table. (5.2)
- Liver enzyme abnormalities: Persistent elevations in hepatic transaminase can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter. (5.3)
- There have been postmarketing reports of acute renal failure, sometimes requiring dialysis, in patients treated with sitagliptin. Assessment of renal function is recommended prior to initiation of JUVISYNC and periodically thereafter. (5.4, 6.2)
- There is an increased risk of hypoglycemia when JUVISYNC is added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia. (2.3, 5.5)
- There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop JUVISYNC, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment. (5.6, 6.2)

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

Most common adverse reactions (incidence ≥5%) with simvastatin are: upper respiratory infection, headache, abdominal pain, constipation, and nausea. Adverse reactions reported in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo. (6.1)

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

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

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.4, 4, 5.2, 7.1, 7.2, 7.3, 12.3)

Interacting Agents	Prescribing Recommendations
Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, nefazodone), gemfibrozil, cyclosporine, danazol	Contraindicated with JUVISYNC

Verapamil, diltiazem, dronedarone	Do not exceed 10 mg simvastatin (100 mg/10 mg or 50 mg/10 mg JUVISYNC) daily
Amiodarone, amlodipine, ranolazine	Do not exceed 20 mg simvastatin (100 mg/20 mg or 50 mg/20 mg JUVISYNC) daily
Grapefruit juice	Avoid grapefruit juice

- Coumarin anticoagulants: Concomitant use with simvastatin prolongs INR. Achieve stable INR prior to starting JUVISYNC. Monitor INR frequently until stable upon initiation or alteration of JUVISYNC therapy. (7.6)
- Other lipid-lowering medications: Use with other fibrate products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with JUVISYNC. (5.2, 7.2, 7.4).

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

- Safety and effectiveness of JUVISYNC in children under 18 years have not been established. (8.4)
- There are no adequate and well-controlled studies in pregnant women. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

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