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.

Revised: XX/XXXX

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

1.1 Sitagliptin

Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. *[See Clinical Studies (14.1).]*

1.2 Simvastatin

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. In patients with coronary heart disease (CHD) or at high risk of CHD, simvastatin can be started simultaneously with diet.

Reductions in Risk of CHD Mortality and Cardiovascular Events

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 is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

Hyperlipidemia

Simvastatin is indicated to:

- Reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia (Fredrickson type IIa, heterozygous familial and nonfamilial) or mixed dyslipidemia (Fredrickson type IIb).
- Reduce elevated TG in patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- Reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- Reduce 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 Important Limitations of Use

JUVISYNC should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

JUVISYNC has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JUVISYNC. *[See Warnings and Precautions (5.1).]*

JUVISYNC has not been studied in conditions where the major abnormality is elevation of chylomicrons (i.e., hyperlipidemia Fredrickson types I and V).

Because doses of JUVISYNC appropriate for patients with severe renal impairment (CrCl <30 mL/min, approximately corresponding to serum creatinine levels of >3.0 mg/dL in men and >2.5 mg/dL in women) or end-stage renal disease (ESRD) are not available in this combination product, JUVISYNC is not recommended in patients with severe renal impairment or ESRD.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The dosages for therapy with JUVISYNC 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 (sitagliptin/simvastatin) once daily. JUVISYNC should be taken as a single daily dose in the evening. JUVISYNC should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing.

The recommended starting dose is 100 mg/40 mg per day. For patients already taking simvastatin (10, 20, or 40 mg daily) with or without sitagliptin 100 mg daily, JUVISYNC may be initiated at the dose of 100 mg sitagliptin and the dose of simvastatin already being taken.

After initiation or titration of JUVISYNC, lipid levels may be analyzed after 4 or more weeks and dosage adjusted, if needed.

2.2 Patients with Renal Impairment

JUVISYNC is not recommended in patients with severe renal impairment or ESRD. JUVISYNC can be used in patients with normal renal function or mild renal impairment (creatinine clearance [CrCl] greater than or equal to 50 mL/min, approximately corresponding to serum creatinine levels of less than or equal to 1.7 mg/dL in men and less than or equal to 1.5 mg/dL in women), without adjustment of the sitagliptin dose. Because simvastatin does not undergo significant renal excretion, modification of the dose of the simvastatin component should not be necessary in patients with mild renal impairment.

For patients with moderate renal impairment (CrCl greater than or equal to 30 to less than 50 mL/min, approximately corresponding to serum creatinine levels of greater than 1.7 to less than or equal to 3.0 mg/dL in men and greater than 1.5 to less than or equal to 2.5 mg/dL in women), the recommended starting dose of JUVISYNC is 50 mg/40 mg once daily. For patients with moderate renal impairment who are already taking simvastatin (10, 20, or 40 mg daily) with or without sitagliptin 50 mg

daily, JUVISYNC may be initiated at the dose of 50 mg sitagliptin and the dose of simvastatin already being taken.

Assessment of renal function is recommended prior to initiation of JUVISYNC and periodically thereafter. Creatinine clearance can be estimated from serum creatinine using the Cockcroft-Gault formula. *[See Warnings and Precautions (5.4); Clinical Pharmacology (12.3).]* There have been postmarketing reports of worsening renal function in patients with renal impairment treated with sitagliptin, some of whom were prescribed inappropriate doses of sitagliptin.

2.3 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When JUVISYNC is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia. *[See Warnings and Precautions (5.5).]*

2.4 Coadministration with Other Drugs

Patients taking Verapamil, Diltiazem, or Dronedarone

- The dose of simvastatin should not exceed 10 mg per day (100 mg/10 mg or 50 mg/10 mg per day of JUVISYNC) *[see Warnings and Precautions (5.2); Drug Interactions (7.3); Clinical Pharmacology (12.3)].*

Patients taking Amiodarone, Amlodipine or Ranolazine

- The dose of simvastatin should not exceed 20 mg per day (100 mg/20 mg or 50 mg/20 mg per day of JUVISYNC) *[see Warnings and Precautions (5.2); Drug Interactions (7.3); Clinical Pharmacology (12.3)].*

2.5 Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage is 100 mg/40 mg (for patients with normal or mildly impaired renal function) or 50 mg/40 mg (for patients with moderately impaired renal function) per day in the evening. JUVISYNC should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.6 Chinese Patients Taking Lipid-Modifying Doses (greater than or equal to 1 g/day Niacin) of Niacin-Containing Products

Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses (greater than or equal to 1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with JUVISYNC 100 mg/40 mg or 50 mg/40 mg per day coadministered with lipid-modifying doses of niacin-containing products. The cause of the increased risk of myopathy is not known. It is also unknown if the risk for myopathy with coadministration of JUVISYNC with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients. *[See Warnings and Precautions (5.2).]*

3 DOSAGE FORMS AND STRENGTHS

- JUVISYNC 100 mg/10 mg tablets are pink-beige, bi-convex round, film-coated tablets, coded with the Merck logo and "753" on one side and plain on the other.
- JUVISYNC 100 mg/20 mg tablets are pink-beige, bi-convex modified capsule-shaped, film-coated tablets, coded with the Merck logo and "757" on one side and plain on the other.
- JUVISYNC 100 mg/40 mg tablets are orange-beige, bi-convex modified capsule-shaped, film-coated tablets, coded with the Merck logo and "773" on one side and plain on the other.
- JUVISYNC 50 mg/10 mg tablets are red, bi-convex modified capsule-shaped, film-coated tablets, coded with the Merck logo and "533" on one side and plain on the other.
- JUVISYNC 50 mg/20 mg tablets are orange-beige, bi-convex modified capsule-shaped, film-coated tablets, coded with the Merck logo and "535" on one side and plain on the other.
- JUVISYNC 50 mg/40 mg tablets are red, bi-convex modified capsule-shaped, film-coated tablets, coded with the Merck logo and "537" on one side and plain on the other.

4 CONTRAINDICATIONS

JUVISYNC is contraindicated in the following conditions:

- History of a serious hypersensitivity reaction, such as anaphylaxis or angioedema, to any component of this medication. *[See Warnings and Precautions (5.6); Adverse Reactions (6.2).]*

- Concomitant administration of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) *[see Warnings and Precautions (5.2)]*.
- Concomitant administration of gemfibrozil, cyclosporine, or danazol *[see Warnings and Precautions (5.2)]*.
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels *[see Warnings and Precautions (5.3)]*.
- 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) decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, simvastatin 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 use with JUVISYNC 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. **JUVISYNC 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, JUVISYNC 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. Because statins have the potential for serious adverse reactions in nursing infants, women who require treatment with JUVISYNC should not breastfeed their infants. A small amount of another drug in the statin class passes into breast milk. It is not known whether simvastatin is excreted into human milk *[see Use in Specific Populations (8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin. After initiation of JUVISYNC, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, JUVISYNC should promptly be discontinued and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using JUVISYNC. *[See also Adverse Reactions (6.2).]*

5.2 Myopathy/Rhabdomyolysis

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (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), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy, including rhabdomyolysis, is dose related. In a clinical trial database in which 41,413 patients were treated with simvastatin, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03% and 0.08% at 20 and 40 mg/day, respectively. The incidence of myopathy with 80 mg (0.61%) was disproportionately higher than that observed at the lower doses. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with simvastatin (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 20 mg/day was approximately 0.02%; in patients treated with 80 mg/day, the incidence was 0.9%. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 20 mg/day was 0%; in patients on 80 mg/day, the incidence was approximately 0.4%. The incidence of myopathy,

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