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 lV hyperlipidemia).
- Reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia (Fredrickson type lll hyperlipidemia).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) 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 must not be split or divided 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.

Simvastatin exposure is approximately doubled with concomitant use of lomitapide; therefore, the dose of simvastatin should be reduced by 50% if initiating lomitapide. For patients with normal or mildly impaired renal function, JUVISYNC dosage should not exceed 100 mg/20 mg daily (or 100 mg/40 mg daily for patients who have previously taken simvastatin 80 mg daily chronically, e.g., for 12 months or more, without evidence of muscle toxicity) while taking lomitapide. For patients with moderately impaired renal function, JUVISYNC dosage should not exceed 50 mg/20 mg daily (or 50 mg/40 mg daily for patients who have previously taken simvastatin 80 mg daily chronically, e.g., for 12 months or more, without evidence of muscle toxicity) while taking lomitapide.

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, nefazodone, and cobicistat-containing products) *[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, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

All patients starting therapy with JUVISYNC, or whose dose of JUVISYNC is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing JUVISYNC. JUVISYNC therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with JUVISYNC 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 impairment usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. JUVISYNC therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. JUVISYNC therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

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 which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, posaconazole, and voriconazole, the macrolide antibiotics erythromycin and clarithromycin, the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, the antidepressant nefazodone, cobicistat-containing products, and grapefruit juice *[see Clinical Pharmacology (12.3)]*. Combination of these drugs with JUVISYNC is contraindicated. If short-term treatment with strong CYP3A4 inhibitors is unavoidable, therapy with JUVISYNC must be suspended during the course of treatment. *[See Contraindications (4); Drug Interactions (7.1).]*

The combined use of JUVISYNC with gemfibrozil, cyclosporine, or danazol is contraindicated *[see Contraindications (4); Drug Interactions (7.1, 7.2)].*

Caution should be used when prescribing other fibrates with JUVISYNC, as these agents can cause myopathy when given alone and the risk is increased when they are coadministered *[see Drug Interactions (7.2)]*.

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing JUVISYNC with colchicine *[see Drug Interactions (7.7)]*.

The benefits of the combined use of JUVISYNC with the following drugs should be carefully weighed against the potential risks of combinations: amiodarone, dronedarone, verapamil, diltiazem, amlodipine, ranolazine and lipid-lowering drugs other than gemfibrozil (other fibrates, ≥1 g/day of niacin, or, for patients with HoFH, lomitapide), *[see Drug Interactions (7.2, 7.3, 7.4); Table 6 in Clinical Pharmacology (12.3)] [also see Dosage and Administration, Patients with Homozygous Familial Hypercholesterolemia (2.5)]*.

Cases of myopathy, including rhabdomyolysis, have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In an ongoing, double-blind, randomized cardiovascular outcomes trial, an independent safety monitoring committee identified that the incidence of myopathy is higher in Chinese compared with non-Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses of a niacin-containing product. 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. It is 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 Drug Interactions (7.4)]*.

Prescribing recommendations for interacting agents are summarized in Table 1 *[see also Dosage and Administration (2.4, 2.5); Drug Interactions (7.1, 7.2, 7.3); Clinical Pharmacology (12.3)]*.

Table 1: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Strong CYP3A4 Inhibitors, e.g.: Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Cobicistat-containing products 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
Lomitapide	For patients with HoFH, do not exceed 20 mg simvastatin (100 mg/20 mg or 50 mg/20 mg JUVISYNC) daily*
Grapefruit juice	Avoid grapefruit juice

* For patients with HoFH who have been taking 80 mg simvastatin chronically (e.g., for 12 months or more) without evidence of muscle toxicity, do not exceed 40 mg simvastatin when taking lomitapide.

5.3 Liver Dysfunction

Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In the Scandinavian Simvastatin Survival Study (4S) *[see Clinical Studies (14.2)]*, the number of patients with more than one transaminase elevation to >3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated

Table 17: Mean Response in Patients with Primary Hyperlipidemia and Combined (mixed) Hyperlipidemia (Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG*
Lower Dose Comparative Study[†] (Mean % Change at Week 6)					
Simvastatin 5 mg q.p.m.	109	-19	-26	10	-12
Simvastatin 10 mg q.p.m.	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study[‡] (Mean % Change at Week 6)					
Placebo	2223	-1	-1	0	-2
Simvastatin 20 mg q.p.m.	2221	-28	-38	8	-19
Upper Dose Comparative Study[§,¶] (Mean % Change Averaged at Weeks 18 and 24)					
Simvastatin 40 mg q.p.m.	433	-31	-41	9	-18
Multi-Center Combined Hyperlipidemia Study[#] (Mean % Change at Week 6)					
Placebo	125	1	2	3	-4
Simvastatin 40 mg q.p.m.	123	-25	-29	13	-28

* median percent change
† mean baseline LDL-C 244 mg/dL and median baseline TG 168 mg/dL
‡ mean baseline LDL-C 188 mg/dL and median baseline TG 128 mg/dL
§ mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL
¶ Study also included another treatment arm receiving a different dose of simvastatin; baseline mean LDL-C and median TG values were calculated across all treatment arms in study
# mean baseline LDL-C 156 mg/dL and median baseline TG 391 mg/dL.

Hypertriglyceridemia (Fredrickson type IV)

The results of a subgroup analysis in 74 patients with type IV hyperlipidemia from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 18.

Table 18: Six-Week, Lipid-Lowering Effects of Simvastatin in Type IV Hyperlipidemia Median Percent Change (25th and 75th percentile) from Baseline*

TREATMENT	N	Total-C	LDL-C	HDL-C	TG	VLDL-C	Non-HDL-C
Placebo	74	+2 (-7, +7)	+1 (-8, +14)	+3 (-3, +10)	-9 (-25, +13)	-7 (-25, +11)	+1 (-9, +8)
Simvastatin 40 mg/day	74	-25 (-34, -19)	-28 (-40, -17)	+11 (+5, +23)	-29 (-43, -16)	-37 (-54, -23)	-32 (-42, -23)

* The median baseline values (mg/dL) for the patients in this study were: total-C = 254, LDL-C = 135, HDL-C = 36, TG = 404, VLDL-C = 83, and non-HDL-C = 215.

Dysbetalipoproteinemia (Fredrickson type lll)

The results of a subgroup analysis in 7 patients with type lll hyperlipidemia (dysbetalipoproteinemia) (apo E2/2) (VLDL-C/TG>0.25) from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 19.

Table 19: Six-Week, Lipid-Lowering Effects of Simvastatin in Type lll Hyperlipidemia Median Percent Change (min, max) from Baseline*

TREATMENT	N	Total-C	LDL-C + IDL	HDL-C	TG	VLDL-C + IDL	Non-HDL-C
Placebo	7	-8 (-24, +34)	-8 (-27, +23)	-2 (-21, +16)	+4 (-22, +90)	-4 (-28, +78)	-8 (-26, -39)
Simvastatin 40 mg/day	7	-50 (-66, -39)	-50 (-60, -31)	+7 (-8, +23)	-41 (-74, -16)	-58 (-90, -37)	-57 (-72, -44)

* The median baseline values (mg/dL) were: total-C = 324, LDL-C = 121, HDL-C = 31, TG = 411, VLDL-C = 170, and non-HDL-C = 291.

Homozygous Familial Hypercholesterolemia

In a controlled clinical study, 4 patients, 19-27 years of age, with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses. Reductions in LDL-C were observed for all patients. The mean LDL-C reduction for the 40 mg dose was 14% (range 8% to 23%, median 12%).

Endocrine Function

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other statins and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled, 12-week study there was no significant effect of simvastatin 80 mg on the plasma testosterone response to human chorionic gonadotropin. In another 24-week study, simvastatin 20-40 mg had no detectable effect on spermatogenesis. In 4S, in which 4444 patients were randomized to simvastatin 20-40 mg/day or placebo for a median duration of 5.4 years, the incidence of male sexual adverse events in the two treatment groups was not significantly different. Because of these factors, the small changes in plasma testosterone are unlikely to be clinically significant. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown.

16 HOW SUPPLIED/STORAGE AND HANDLING

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. They are supplied as follows:

NDC 0006-0753-31 unit of use bottles of 30

NDC 0006-0753-54 unit of use bottles of 90

NDC 0006-0753-82 bottles of 1000.

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. They are supplied as follows:

NDC 0006-0757-31 unit of use bottles of 30

NDC 0006-0757-54 unit of use bottles of 90

NDC 0006-0757-82 bottles of 1000.

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. They are supplied as follows:

NDC 0006-0773-31 unit of use bottles of 30

NDC 0006-0773-54 unit of use bottles of 90

NDC 0006-0773-82 bottles of 1000.

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. They are supplied as follows:

NDC 0006-0533-31 unit of use bottles of 30

NDC 0006-0533-54 unit of use bottles of 90

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. They are supplied as follows:

NDC 0006-0535-31 unit of use bottles of 30

NDC 0006-0535-54 unit of use bottles of 90

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. They are supplied as follows:

NDC 0006-0537-31 unit of use bottles of 30

NDC 0006-0537-54 unit of use bottles of 90

Storage

Store at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Store in a dry place with cap tightly closed.

Storage of 1000 count bottles

Dispense into a USP tightly closed, moisture-resistant container.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide).

17.1 Instructions

Patients should be informed of the potential risks and benefits of JUVISYNC and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Patients should be informed that acute pancreatitis has been reported during postmarketing use of sitagliptin. Patients should be informed that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue JUVISYNC and contact their physician if persistent severe abdominal pain occurs *[see Warnings and Precautions (5.1)].*

Patients should be informed that the incidence of hypoglycemia is increased when sitagliptin is added to a sulfonylurea or insulin and that a lower dose of the sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

Patients should be informed that allergic reactions have been reported during postmarketing use of sitagliptin. If symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking JUVISYNC and seek medical advice promptly.

Patients should be informed that the tablets must never be split or divided before swallowing.

Physicians should instruct their patients to read the Medication Guide before starting JUVISYNC therapy and to reread each time the prescription is renewed. Patients should be instructed to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

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 JUVISYNC *[see Contraindications (4); Warnings and Precautions (5.2)]*. Patients should also be advised to inform other healthcare professionals prescribing a new medication or increasing the dose of an existing medication that they are taking JUVISYNC.

17.2 Laboratory Tests

Patients should be informed that response to JUVISYNC should be monitored by periodic measurements of blood glucose, A1C, and cholesterol levels, with a goal of decreasing these levels towards the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients

should be informed of the potential need to adjust the dose or discontinue JUVISYNC based on changes in renal function test results over time.

It is recommended that liver function tests be performed before the initiation of JUVISYNC, and thereafter when clinically indicated. All patients treated with JUVISYNC should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.

17.3 Muscle Pain

All patients starting therapy with JUVISYNC should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing JUVISYNC. The risk of myopathy, including rhabdomyolysis, occurring with use of JUVISYNC is increased when taking certain types of medication or consuming grapefruit juice. Patients should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.4 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using JUVISYNC. Discuss future pregnancy plans with your patients, and discuss when to stop taking JUVISYNC if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking JUVISYNC and call their healthcare professional.

17.5 Breastfeeding

Women who are breastfeeding should not use JUVISYNC. Patients who have a lipid disorder and are breastfeeding should be advised to discuss the options with their healthcare professional.

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Manufactured by:
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Medication Guide
JUVISYNC™ (JU-vih-sink)
(sitagliptin and simvastatin)
Tablets

Read this Medication Guide carefully before you start taking JUVISYNC and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about JUVISYNC, ask your doctor or pharmacist.

What is the most important information I should know about JUVISYNC?

Serious side effects can happen in people taking JUVISYNC, including inflammation of the pancreas (pancreatitis) which may be severe and lead to death. Certain medical problems make you more likely to get pancreatitis.

Before you start taking JUVISYNC:
Tell your doctor if you have ever had

- pancreatitis
- stones in your gallbladder (gallstones)
- a history of alcoholism
- high blood triglyceride levels
- kidney problems

Stop taking JUVISYNC and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

What is JUVISYNC?

- JUVISYNC is a prescription medicine that contains two medicines, sitagliptin and simvastatin, in one pill. JUVISYNC can be used in adults who need both sitagliptin and simvastatin.
- Sitagliptin can be used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
- Simvastatin can be used with diet and exercise in adults at high risk for heart attack or stroke to lower your chance of:
  - death from heart problems
  - having a heart attack or stroke
  - needing certain blood vessel procedures
- Simvastatin can be used in adults with certain cholesterol problems to lower levels of total cholesterol, LDL (bad) cholesterol, and fatty substances called triglycerides in the blood. In addition, simvastatin raises levels of HDL (good) cholesterol. Simvastatin is for people who cannot control their cholesterol levels by diet and exercise alone. You should stay on a cholesterol-lowering diet while taking this medicine.
- Sitagliptin is not for people with type 1 diabetes.
- Sitagliptin is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- If you have had inflammation of your pancreas (pancreatitis) in the past, it is not known if you have a higher chance of getting pancreatitis while you take sitagliptin.
- JUVISYNC has not been studied in people who have an increase of chylomicrons (Fredrickson types I and V).
- JUVISYNC is not for people with certain kidney problems.
- It is not known if JUVISYNC is safe and effective when used in children under 18 years of age.

For more information, see the sections called "**What is type 2 diabetes?**" and "**What should I know about high cholesterol?**".

Who should not take JUVISYNC?

Do not take JUVISYNC if you:

- are allergic to any of the ingredients in JUVISYNC. See the end of this Medication Guide for a complete list of ingredients in JUVISYNC.

  Symptoms of a serious allergic reaction to JUVISYNC may include:
  - rash
  - raised red patches on your skin (hives)
  - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing
- take certain medicines such as:
  - anti-fungal medicines including:
    - itraconazole
    - ketoconazole
    - posaconazole
    - voriconazole
  - HIV protease inhibitors, including:
    - indinavir
    - nelfinavir
    - ritonavir
    - saquinavir
    - tipranavir
    - atazanavir
  - certain hepatitis C virus protease inhibitors, including:
    - boceprevir
    - telaprevir
  - certain antibiotics, including:
    - erythromycin
    - clarithromycin
    - telithromycin
  - nefazodone
  - medicines containing cobicistat
  - a fibrate medicine for lowering cholesterol called gemfibrozil
  - cyclosporine
  - danazol

  Ask your doctor if you are not sure whether your medicine is listed above.

- have active liver disease or repeated blood tests indicating possible liver problems.
- are pregnant or think you may be pregnant, or you are planning to become pregnant.
- are a woman of childbearing age, you should use an effective method of birth control to prevent pregnancy while using JUVISYNC.
- are breastfeeding or plan to breastfeed.

What should I tell my doctor before taking JUVISYNC?

Before you take JUVISYNC, tell your doctor if you:

- have or have had inflammation of your pancreas (pancreatitis).

- have kidney problems.
- drink substantial quantities of alcohol or ever had liver problems.
- have any other medical conditions.
- are taking drugs that prevent blood clots, such as warfarin.

Taking JUVISYNC with certain substances can increase the risk of muscle problems. It is especially important to tell your doctor if you take:

- fibric acid derivatives (such as fenofibrate)
- amiodarone or dronedarone (drugs used to treat an irregular heartbeat)
- the following medicines used to treat high blood pressure, chest pain with heart disease, or other heart problems:
  - verapamil
  - diltiazem
  - amlodipine
  - ranolazine
- grapefruit juice (which should be avoided while taking JUVISYNC)
- colchicine (a medicine used to treat gout)
- lomitapide (a medicine used to treat a serious and rare genetic cholesterol condition)
- large doses of niacin or nicotinic acid

Tell your doctor if you are taking niacin or a niacin-containing product, as this may increase your risk of muscle problems, especially if you are Chinese.

Tell all of your doctors about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take JUVISYNC?

- Take one JUVISYNC tablet each day, in the evening, exactly as your doctor tells you.
- Do not break or cut JUVISYNC tablets before swallowing. If you cannot swallow JUVISYNC tablets whole, tell your doctor.
- Your doctor may tell you to take JUVISYNC along with other diabetes medicines. Low blood sugar can happen more often when JUVISYNC is taken with certain other diabetes medicines. See "**What are the possible side effects of JUVISYNC?**".
- If you take too much JUVISYNC, call your doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JUVISYNC.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.
- Your doctor will monitor your condition with regular blood tests, including your blood sugar levels, hemoglobin A1C, and cholesterol levels, and to check for side effects.
- Your doctor will do blood tests to check how well your kidneys are working before and during your treatment with JUVISYNC. Your doctor may change your dose or discontinue JUVISYNC based on the results of your blood tests.

What are the possible side effects of JUVISYNC?

Serious side effects have happened in people taking JUVISYNC.

- See "**What is the most important information I should know about JUVISYNC?**".

- **myopathy (muscle weakness) and rhabdomyolysis (muscle breakdown).** Tell your doctor right away if you have unexplained muscle pain, tenderness, or weakness especially with fever while you take JUVISYNC.

    - Muscle problems, including muscle breakdown, can be serious in some people and on rare occasions may cause kidney damage that can lead to death.
    - The risk of muscle breakdown is greater at higher doses of JUVISYNC.
    - The risk of muscle breakdown is greater in people 65 years of age and older, females, and people with kidney or thyroid problems.

    If you have muscle problems that do not go away even after your doctor has advised you to stop taking JUVISYNC, notify your doctor. Your doctor may do further tests to diagnose the cause of your muscle problems.

- **liver problems.** Your doctor should do blood tests to check your liver before you start taking JUVISYNC and if you have any symptoms of liver problems while you take JUVISYNC. Call your doctor right away if you have the following symptoms of liver problems:

    - feel tired or weak
    - loss of appetite
    - upper belly pain
    - dark urine
    - yellowing of your skin or the whites of your eyes

- **kidney problems**, sometimes requiring dialysis
- **low blood sugar (hypoglycemia).** If you take JUVISYNC with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you use JUVISYNC. Signs and symptoms of low blood sugar may include:

    - headache
    - drowsiness
    - weakness
    - dizziness
    - confusion
    - irritability
    - hunger
    - fast heart beat
    - sweating
    - feeling jittery

- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JUVISYNC and call your doctor right away. See "**Who should not take JUVISYNC?**". Your doctor may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.

The most common side effects of JUVISYNC include:

- upper respiratory infection
- stuffy or runny nose and sore throat
- headache
- stomach pain

- constipation
- nausea

JUVISYNC may have other side effects, including:

- swelling of the hands or legs. Swelling of the hands or legs can happen if you take JUVISYNC in combination with rosiglitazone (Avandia®). Rosiglitazone is another type of diabetes medicine.
- joint pain
- muscle pain
- alterations in some laboratory blood tests
- liver problems (sometimes serious)
- nausea
- dizziness
- tingling sensation
- depression
- trouble sleeping
- poor memory
- erectile dysfunction
- breathing problems including persistent cough and/or shortness of breath or fever.

These are not all the possible side effects of JUVISYNC. For more information, ask your doctor or pharmacist.

Tell your doctor if you have any side effect that bothers you, is unusual or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JUVISYNC?

Store JUVISYNC at 68°F to 77°F (20°C to 25°C). Store in a dry place with cap tightly closed.

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

General information about the use of JUVISYNC

Medicines are sometimes prescribed for purposes that are not listed in Medication Guides. Do not use JUVISYNC for a condition for which it was not prescribed. Do not give JUVISYNC to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about JUVISYNC. If you would like to know more information, talk with your doctor. You can ask your doctor or pharmacist for additional information about JUVISYNC that is written for health professionals. For more information, go to www.JUVISYNC.com or call 1-800-622-4477.

What are the ingredients in JUVISYNC?

Active ingredients: sitagliptin and simvastatin

Inactive ingredients: anhydrous dibasic calcium phosphate, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, magnesium stearate, ascorbic acid, citric acid monohydrate, lactose monohydrate, pre-gelatinized corn starch, butylated hydroxyanisole. The tablet film coating contains the

following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and red iron oxide. The film coating for certain tablet strengths also contains yellow iron oxide and black iron oxide.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.

High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

What should I know about high cholesterol?

Cholesterol is a type of fat found in your blood. Cholesterol comes from two sources. It is produced by your body and it comes from the food you eat. Your total cholesterol is made up of both LDL and HDL cholesterol.

LDL cholesterol is called "bad" cholesterol because it can build up in the wall of your arteries and form plaque, which can slow or block blood flow to your heart, brain, and other organs.

HDL cholesterol is called "good" cholesterol because it keeps the bad cholesterol from building up in the arteries.

Triglycerides also are fats found in your body.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.