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

----------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 moderate or severe renal impairment who require sitagliptin 50 or 25 mg should not use JUVISYNC due to the unavailability of these dosage strengths for JUVISYNC. (1.3)

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

- Doses are 100 mg/10 mg, 100 mg/20 mg, and 100 mg/40 mg per day. (2.1)
- Recommended usual starting dose is 100 mg/40 mg once a day in the evening. (2.1)
- Patients already taking simvastatin (10, 20, or 40 mg) can initiate JUVISYNC at a dose of 100 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, and 100 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 symptoms of myopathy. 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
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol	Contraindicated with JUVISYNC
Verapamil, diltiazem	Do not exceed 100 mg/10 mg JUVISYNC daily
Amiodarone, amlodipine, ranolazine	Do not exceed 100 mg/20 mg JUVISYNC daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

- 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: 10/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Sitagliptin
1.2 Simvastatin
1.3 Important Limitations of Use
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
2.2 Patients with Renal Impairment
2.3 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin
2.4 Coadministration with Other Drugs
2.5 Patients with Homozygous Familial Hypercholesterolemia
2.6 Chinese Patients Taking Lipid-Modifying Doses (≥1 g/day Niacin) of Niacin-Containing Products
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Pancreatitis
5.2 Myopathy/Rhabdomyolysis
5.3 Liver Dysfunction
5.4 Renal Impairment
5.5 Use with Medications Known to Cause Hypoglycemia
5.6 Hypersensitivity Reactions
5.7 Endocrine Function
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Strong CYP3A4 Inhibitors, Cyclosporine, or Danazol
7.2 Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone
7.3 Amiodarone, Ranolazine, or Calcium Channel Blockers
7.4 Niacin
7.5 Digoxin
7.6 Coumarin Anticoagulants
7.7 Colchicine
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Sitagliptin Clinical Studies
14.2 Simvastatin Clinical Studies
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Instructions
17.2 Laboratory Tests
17.3 Muscle Pain
17.4 Pregnancy
17.5 Breastfeeding

*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 moderate or severe renal impairment (CrCl <50 mL/min, approximately corresponding to serum creatinine levels of >1.7 mg/dL in men and >1.5 mg/dL in women) or end-stage renal disease (ESRD) are not available in this combination product, JUVISYNC is not recommended in patients with moderate or 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, and 100 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 moderate or severe renal impairment or ESRD. JUVISYNC can be used in patients with normal renal function or mild renal impairment (creatinine clearance [CrCl] ≥50 mL/min, approximately corresponding to serum creatinine levels of ≤1.7 mg/dL in men and ≤1.5 mg/dL in women). 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.

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, or Diltiazem

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

Patients taking Amiodarone, Amlodipine or Ranolazine

- The dose of JUVISYNC should not exceed 100 mg/20 mg per day *[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 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 (≥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 (≥1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with JUVISYNC 100 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.

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, HIV protease inhibitors, 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, 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.

All patients starting therapy with JUVISYNC, or whose dose of simvastatin 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. 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 of simvastatin is being increased. 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, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, the ketolide antibiotic telithromycin, HIV protease inhibitors, the antidepressant nefazodone, and large quantities of grapefruit juice (>1 quart daily). Combination of these drugs with JUVISYNC is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin,

clarithromycin or telithromycin is unavoidable, therapy with JUVISYNC must be suspended during the course of treatment. *[See Contraindications (4); Drug Interactions (7.1).] In vitro* studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the JUVISYNC dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with JUVISYNC. *[See 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, verapamil, diltiazem, amlodipine, ranolazine and lipid-lowering drugs other than gemfibrozil (other fibrates or ≥1 g/day of niacin), *[see Drug Interactions (7.2, 7.3, 7.4); Table 3 in Clinical Pharmacology (12.3)]*.

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 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); 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
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Gemfibrozil Cyclosporine Danazol	Contraindicated with JUVISYNC
Verapamil Diltiazem	Do not exceed 100 mg/10 mg JUVISYNC daily
Amiodarone Amlodipine Ranolazine	Do not exceed 100 mg/20 mg JUVISYNC daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

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 transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2221) and 5 in the placebo group (n=2223). Of the 1986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, 8 (0.4%) developed consecutive LFT elevations to >3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40 and 80 mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including simvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with JUVISYNC, promptly interrupt therapy. If an alternate etiology is not found do not restart JUVISYNC. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy *[see Warnings and Precautions (5.2)].*

The drug 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 transaminase elevations are contraindications to the use of JUVISYNC.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment. *[See also Adverse Reactions (6.1).]*

5.4 Renal Impairment

Assessment of renal function is recommended prior to initiating JUVISYNC and periodically thereafter. JUVISYNC is not recommended for use in patients with moderate or severe renal impairment or ESRD because doses of JUVISYNC appropriate for patients with moderate or severe renal impairment or ESRD are not available in this combination product. *[See Dosage and Administration (2.2); Clinical Pharmacology (12.3).]*

There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis, in patients treated with sitagliptin. A subset of these reports involved patients with renal impairment, some of whom were prescribed inappropriate doses of sitagliptin. A return to baseline levels of renal impairment has been observed with supportive treatment and discontinuation of potentially causative agents.

Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials.

5.5 Use with Medications Known to Cause Hypoglycemia

When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. *[See Adverse Reactions (6.1).]* Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia. *[See Dosage and Administration (2.3).]*

5.6 Hypersensitivity Reactions

[See also Adverse Reactions (6.2).]

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose.

If a hypersensitivity reaction is suspected, discontinue JUVISYNC, assess for other potential causes for the event, and institute alternative treatment.

Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with JUVISYNC.

5.7 Endocrine Function

Increases in A1C and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including simvastatin.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

JUVISYNC

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a pooled subgroup analysis of 19 controlled clinical studies of sitagliptin involving 1582 patients whose background therapy included simvastatin, incidences of adverse reactions for patients treated with sitagliptin and simvastatin (n=827) were similar to those for patients treated with control therapy (placebo or active comparator) and simvastatin (n=755). Among these patients, 3.3% of the sitagliptin-treated group and 4.2% of controls discontinued due to adverse reactions.

Sitagliptin

In controlled clinical studies as both monotherapy and combination therapy with metformin, pioglitazone, or rosiglitazone and metformin, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with sitagliptin were similar to placebo. In combination with glimepiride, with or without metformin, the overall incidence of clinical adverse reactions with sitagliptin was higher than with placebo, in part related to a higher incidence of hypoglycemia (see Table 4); the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with sitagliptin 100 mg daily, sitagliptin 200 mg daily, and placebo. Five placebo-controlled add-on combination therapy studies were also conducted: one with metformin; one with pioglitazone; one with metformin and rosiglitazone; one with glimepiride (with or without metformin); and one with insulin (with or without metformin). In these trials, patients with inadequate glycemic control on a stable dose of the background therapy were randomized to add-on therapy with sitagliptin 100 mg daily or placebo. The adverse reactions, excluding hypoglycemia, reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin 100 mg daily and more commonly than in patients treated with placebo, are shown in Table 2 for the clinical trials of at least 18 weeks duration. Incidences of hypoglycemia are shown in Table 4.

Table 2
Placebo-Controlled Clinical Studies of Sitagliptin Monotherapy or Add-on Combination Therapy with Pioglitazone, Metformin + Rosiglitazone, or Glimepiride +/- Metformin: Adverse Reactions (Excluding Hypoglycemia) Reported in ≥5% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality†

	Number of Patients (%)	
Monotherapy (18 or 24 weeks)	**Sitagliptin 100 mg**	**Placebo**
	N = 443	N = 363
Nasopharyngitis	23 (5.2)	12 (3.3)
Combination with Pioglitazone (24 weeks)	**Sitagliptin 100 mg + Pioglitazone**	**Placebo + Pioglitazone**
	N = 175	N = 178
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Headache	9 (5.1)	7 (3.9)
Combination with Metformin + Rosiglitazone (18 weeks)	**Sitagliptin 100 mg + Metformin + Rosiglitazone**	**Placebo + Metformin + Rosiglitazone**
	N = 181	N = 97
Upper Respiratory Tract Infection	10 (5.5)	5 (5.2)
Nasopharyngitis	11 (6.1)	4 (4.1)
Combination with Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Nasopharyngitis	14 (6.3)	10 (4.6)
Headache	13 (5.9)	5 (2.3)

† Intent-to-treat population

In the 24-week study of patients receiving sitagliptin as add-on combination therapy with metformin, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo.

In the 24-week study of patients receiving sitagliptin as add-on therapy to insulin (with or without metformin), there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo, except for hypoglycemia (see Table 4).

In the study of sitagliptin as add-on combination therapy with metformin and rosiglitazone (Table 2), through Week 54 the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the incidence of selected gastrointestinal adverse reactions in patients treated with sitagliptin was as follows: abdominal pain (sitagliptin 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), and diarrhea (3.0%, 2.3%).

In an additional, 24-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients are shown in Table 3.

Table 3
Initial Therapy with Combination of Sitagliptin and Metformin:
Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Metformin alone, Sitagliptin alone, and Placebo)†

	Number of Patients (%)			
	Placebo	**Sitagliptin 100 mg QD**	**Metformin 500 or 1000 mg bid ††**	**Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid ††**
	N = 176	N = 179	N = 364††	N = 372††
Upper Respiratory Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

† Intent-to-treat population.
†† Data pooled for the patients given the lower and higher doses of metformin.

In a 24-week study of initial therapy with sitagliptin in combination with pioglitazone, there were no adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients and more commonly than in patients given pioglitazone alone.

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with sitagliptin.

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control). *[See Warnings and Precautions (5.1).]*

Hypoglycemia

In the sitagliptin clinical trial program, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia. A concurrent blood glucose measurement was not required although most (74%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When sitagliptin was coadministered with a sulfonylurea or with insulin, the percentage of patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo group (Table 4).

Table 4
Incidence and Rate of Hypoglycemia† in Placebo-Controlled Clinical Studies when Sitagliptin was used as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin), Regardless of Investigator Assessment of Causality

Add-On to Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Overall (%)	27 (12.2)	4 (1.8)
Rate (episodes/patient-year)‡	0.59	0.24
Severe (%)§	0 (0.0)	0 (0.0)
Add-On to Insulin (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Insulin (+/- Metformin)**	**Placebo + Insulin (+/- Metformin)**
	N = 322	N = 319
Overall (%)	50 (15.5)	25 (7.8)
Rate (episodes/patient-year)‡	1.06	0.51
Severe (%)§	2 (0.6)	1 (0.3)

† Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.
‡ Based on total number of events (i.e., a single patient may have had multiple events).
§ Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse reactions of hypoglycemia was 1.2% in patients treated with sitagliptin 100 mg and 0.9% in patients treated with placebo.

In the study of sitagliptin as add-on combination therapy with metformin and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on sitagliptin and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on sitagliptin and 1.0% in patients given add-on placebo.

In the 24-week, placebo-controlled factorial study of initial therapy with sitagliptin in combination with metformin, the incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients given sitagliptin alone, 0.8% in patients given metformin alone, and 1.6% in patients given sitagliptin in combination with metformin.

In the study of sitagliptin as initial therapy with pioglitazone, one patient taking sitagliptin experienced a severe episode of hypoglycemia. There were no severe hypoglycemia episodes reported in other studies except in the study involving coadministration with insulin.

Simvastatin

In the pre-marketing controlled clinical studies and their open-label extensions (2423 patients with median duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: gastrointestinal disorders (0.5%), myalgia (0.1%), and arthralgia (0.1%). The most commonly reported adverse reactions (incidence ≥5%) in simvastatin controlled clinical trials were: upper respiratory infections (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6%), and nausea (5.4%).

Scandinavian Simvastatin Survival Study

In 4S involving 4444 patients (age range 35-71 years, 19% women, 100% Caucasians) treated with 20-40 mg/day of simvastatin (n=2221) or placebo (n=2223) over a median of 5.4 years, adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 5.

Table 5
Adverse Reactions Reported Regardless of Causality by ≥2% of Patients Treated with Simvastatin and Greater than Placebo in 4S

	Simvastatin (N = 2221) %	Placebo (N = 2223) %
Body as a Whole		
Edema/swelling	2.7	2.3
Abdominal pain	5.9	5.8
Cardiovascular System Disorders		
Atrial fibrillation	5.7	5.1
Digestive System Disorders		
Constipation	2.2	1.6
Gastritis	4.9	3.9
Endocrine Disorders		
Diabetes mellitus	4.2	3.6
Musculoskeletal Disorders		
Myalgia	3.7	3.2
Nervous System/ Psychiatric Disorders		
Headache	2.5	2.1
Insomnia	4.0	3.8
Vertigo	4.5	4.2
Respiratory System Disorders		
Bronchitis	6.6	6.3
Sinusitis	2.3	1.8
Skin / Skin Appendage Disorders		
Eczema	4.5	3.0
Urogenital System Disorders		
Infection, urinary tract	3.2	3.1

Heart Protection Study

In the Heart Protection Study (HPS), involving 20,536 patients (age range 40-80 years, 25% women, 97% Caucasians, 3% other races) treated with simvastatin 40 mg/day (n=10,269) or placebo (n=10,267) over a mean of 5 years, only serious adverse reactions and discontinuations due to any adverse reactions were recorded. Discontinuation rates due to adverse reactions were 4.8% in patients treated with simvastatin compared with 5.1% in patients treated with placebo. The incidence of myopathy/rhabdomyolysis was <0.1% in patients treated with simvastatin.

Other Clinical Studies

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.

Other adverse reactions reported in clinical trials were: diarrhea, rash, dyspepsia, flatulence, and asthenia.

Laboratory Tests

Sitagliptin

Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with sitagliptin 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs placebo, in four pooled placebo-controlled clinical studies, with a mean baseline WBC count of approximately 6600 cells/microL) is not considered to be clinically relevant. In a 12-week study of 91 patients with chronic renal impairment, 37 patients with moderate renal impairment were randomized to sitagliptin 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were observed in patients treated with sitagliptin [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

Simvastatin

Marked persistent increases of hepatic transaminases have been noted *[see Warnings and Precautions (5.3)]*. Elevated alkaline phosphatase and γ-glutamyl transpeptidase have also been reported. About 5% of patients 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 (5.2).]*

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of sitagliptin (as monotherapy and/or in combination with other antihyperglycemic agents) or simvastatin. Because these 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.

Anemia; depression; headache; dizziness; paresthesia; peripheral neuropathy; interstitial lung disease; pancreatitis; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis *[see Indications and Usage (1.3); Warnings and Precautions (5.1)]*; constipation; vomiting; hepatitis/jaundice; fatal and non-fatal hepatic failure; hepatic enzyme elevations; pruritus; alopecia; a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails); muscle cramps; myalgia; rhabdomyolysis; worsening renal function, including acute renal failure (sometimes requiring dialysis); erectile dysfunction.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome have been reported with sitagliptin *[see Warnings and Precautions (5.6)]*.

An apparent hypersensitivity syndrome has been reported rarely with simvastatin which has included some 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 Strong CYP3A4 Inhibitors, Cyclosporine, or Danazol

Strong CYP3A4 inhibitors: Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of CYP3A4. Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4.

Elevated plasma levels of HMG-CoA reductase inhibitory activity increase the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin. *[See Warnings and Precautions (5.2); Clinical Pharmacology (12.3).]* Concomitant use of drugs labeled as having a strong inhibitory effect on CYP3A4 is contraindicated *[see Contraindications (4)].* If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with JUVISYNC must be suspended during the course of treatment. If JUVISYNC is suspended during treatment with any of these agents, consideration should be given to the use of sitagliptin to maintain glycemic control until JUVISYNC can be reinstated.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of simvastatin. It is recommended that dose adjustment of JUVISYNC be considered during concomitant use of voriconazole and JUVISYNC to reduce the risk of myopathy, including rhabdomyolysis *[see Warnings and Precautions (5.2)].*

Cyclosporine or Danazol: The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of cyclosporine or danazol. Therefore, concomitant use of these drugs is contraindicated *[see Contraindications (4); Warnings and Precautions (5.2); Clinical Pharmacology (12.3)]*.

7.2 Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: Contraindicated with JUVISYNC *[see Contraindications (4); Warnings and Precautions (5.2)].*

Other fibrates: Caution should be used when prescribing with JUVISYNC *[see Warnings and Precautions (5.2)].*

7.3 Amiodarone, Ranolazine, or Calcium Channel Blockers

The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of amiodarone, ranolazine, or calcium channel blockers such as verapamil, diltiazem, or amlodipine *[see Dosage and Administration (2.4); Warnings and Precautions (5.2); Table 3 in Clinical Pharmacology (12.3)]*.

7.4 Niacin

Cases of myopathy, including rhabdomyolysis, have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with JUVISYNC 100 mg/40 mg coadministered with lipid-modifying doses of niacin-containing products. *[See Warnings and Precautions (5.2); Clinical Pharmacology (12.3).]*

7.5 Digoxin

No dosage adjustment of digoxin or JUVISYNC is recommended. Patients receiving digoxin should be monitored.

7.6 Coumarin Anticoagulants

In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, 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 the volunteer and patient studies, 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 JUVISYNC 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 JUVISYNC is changed or JUVISYNC is 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.

7.7 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing JUVISYNC with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [See Contraindications (4).]

JUVISYNC

JUVISYNC 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 use of JUVISYNC 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 decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, JUVISYNC may cause fetal harm when administered to a pregnant woman. If JUVISYNC 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 treatment with JUVISYNC for a lipid disorder, should be advised to use effective contraception. For women trying to conceive, discontinuation of JUVISYNC should be considered. If pregnancy occurs, JUVISYNC should be immediately discontinued.

Sitagliptin

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies in pregnant women.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30- and 20-times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Simvastatin

Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 6 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[1] 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 those expected in the general population. However, the study was only able to exclude a 3- to 4-fold increased risk of congenital anomalies over the background rate. In 89% of these cases, drug treatment was initiated prior to pregnancy and was discontinued during the first trimester when pregnancy was identified.

8.3 Nursing Mothers

JUVISYNC

It is not known whether simvastatin is excreted in human 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 taking JUVISYNC should not nurse their infants. A decision should be made whether to discontinue nursing or discontinue JUVISYNC, taking into account the importance of the drug to the mother *[see Contraindications (4)]*.

Sitagliptin

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness of JUVISYNC in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

JUVISYNC

Because advanced age (≥65 years) is a predisposing factor for myopathy, including rhabdomyolysis, JUVISYNC should be prescribed with caution in the elderly *[see Clinical Pharmacology (12.3)].*

Sitagliptin is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter *[see Dosage and Administration (2.2); Clinical Pharmacology (12.3)]*.

Sitagliptin

Of the total number of subjects (N=3884) in pre-approval clinical safety and efficacy studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Simvastatin

Of the 2423 patients who received simvastatin in Phase III clinical studies and the 10,269 patients in the Heart Protection Study who received simvastatin, 363 (15%) and 5366 (52%), respectively were ≥65 years old. In HPS, 615 (6%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

A pharmacokinetic study with simvastatin showed the mean plasma level of statin activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age. In 4S, 1021 (23%) of 4444 patients were 65 or older. Lipid-lowering efficacy was at least as great in elderly patients compared with younger patients, and simvastatin significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD. In HPS, 52% of patients were elderly (4891 patients 65-69 years and 5806 patients 70 years or older). The relative risk reductions of CHD death, non-fatal MI, coronary and non-coronary revascularization procedures, and stroke were similar in older and younger patients *[see Clinical Studies (14.2)]*. In HPS, among 32,145 patients entering the active run-in period, there were 2 cases of myopathy/rhabdomyolysis; these

patients were aged 67 and 73. Of the 7 cases of myopathy/rhabdomyolysis among 10,269 patients allocated to simvastatin, 4 were aged 65 or more (at baseline), of whom one was over 75. There were no overall differences in safety between older and younger patients in either 4S or HPS.

Because advanced age (≥65 years) is a predisposing factor for myopathy, including rhabdomyolysis, simvastatin should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥65 years of age had an increased risk of myopathy, including rhabdomyolysis, compared to patients <65 years of age. *[See Warnings and Precautions (5.2); Clinical Pharmacology (12.3).]*

8.6 Renal Impairment

JUVISYNC is not recommended for use in patients with moderate or severe renal impairment or ESRD *[see Dosage and Administration (2.2)]*.

8.7 Hepatic Impairment

JUVISYNC is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

10 OVERDOSAGE

Sitagliptin

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg sitagliptin, a mean effect that is not considered clinically important *[see Clinical Pharmacology (12.2)]*. There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as dictated by the patient's clinical status.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

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.

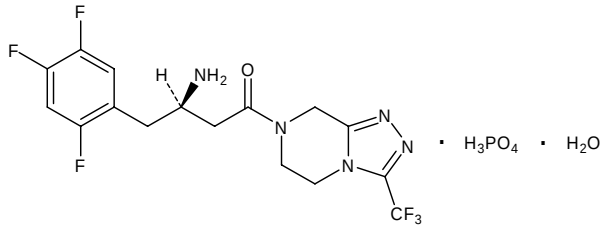
A few cases of overdosage with simvastatin have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. Supportive measures should be taken in the event of an overdose. The dialyzability of simvastatin and its metabolites in man is not known at present.

11 DESCRIPTION

JUVISYNC Tablets contain sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme, and simvastatin, a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*.

Sitagliptin phosphate monohydrate is described chemically as 7-[(3*R*)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine phosphate (1:1) monohydrate.

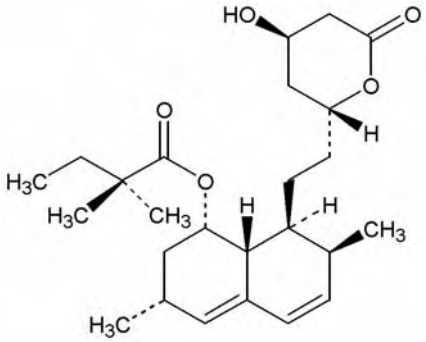
The empirical formula is $C_{16}H_{15}F_6N_5O{\bullet}H_3PO_4{\bullet}H_2O$ and the molecular weight is 523.32. The structural formula is:



Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:



Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Each bilayer tablet of JUVISYNC contains 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 100 mg of free base, either 10 mg, 20 mg, or 40 mg of simvastatin and the following inactive ingredients: anhydrous dibasic calcium phosphate, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, magnesium stearate, ascorbic acid, citric acid monohydrate, lactose monohydrate, and pre-gelatinized corn starch. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, red iron oxide, yellow iron oxide, and black iron oxide. Butylated hydroxyanisole is added as a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sitagliptin

Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by JUVISYNC, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by

intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, JUVISYNC increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity *in vitro* at concentrations approximating those from therapeutic doses.

Simvastatin

Simvastatin is a prodrug and is hydrolyzed to its active β-hydroxyacid 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 VLDL and TG and increases HDL-C.

12.2 Pharmacodynamics

Sitagliptin

General

In patients with type 2 diabetes, administration of sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Coadministration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations. It is unclear how these findings relate to changes in glycemic control in patients with type 2 diabetes.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycemia.

Cardiac Electrophysiology

In a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800 mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline was observed at 3 hours postdose and was 8.0 msec. This increase is not considered to be clinically significant. At the 800 mg dose, peak sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100 mg dose.

In patients with type 2 diabetes administered sitagliptin 100 mg (N=81) or sitagliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

Simvastatin

Epidemiological studies have demonstrated that elevated levels of total-C, LDL-C, as well as decreased levels of HDL-C are associated with the development of atherosclerosis and increased cardiovascular risk. Lowering LDL-C decreases this risk. However, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.3 Pharmacokinetics

General

JUVISYNC

The results of bioequivalence studies in healthy subjects demonstrated that JUVISYNC (sitagliptin and simvastatin) is bioequivalent to coadministration of sitagliptin and simvastatin as individual tablets.

Sitagliptin and simvastatin do not have a clinically meaningful pharmacokinetic interaction.

Absorption

JUVISYNC

A high-fat breakfast did not affect sitagliptin exposure following administration of JUVISYNC, while simvastatin AUC decreased by 24%, simvastatin C_{max} increased by 20%, and simvastatin acid AUC and C_{max} increased by 37% and 116%, respectively. The clinical significance of the above exposure changes in simvastatin and simvastatin acid is not known. JUVISYNC is recommended to be taken in the evening as indicated in simvastatin labeling.

Sitagliptin

The pharmacokinetics of sitagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. After oral administration of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours postdose. Plasma AUC of sitagliptin increased in a dose-proportional manner. Following a single oral 100 mg dose to healthy volunteers, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM, and apparent terminal half-life ($t_{1/2}$) was 12.4 hours. Plasma AUC of sitagliptin increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

The absolute bioavailability of sitagliptin is approximately 87%.

Simvastatin

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid (simvastatin acid), a potent inhibitor of HMG-CoA reductase.

Peak plasma concentrations of simvastatin lactone and simvastatin acid were attained within 1.5 and 4-6 hours postdose, respectively. For simvastatin no substantial deviation from linearity of AUC of inhibitors in the general circulation was observed at doses up to 120 mg.

Distribution

Sitagliptin

The mean volume of distribution at steady state following a single 100 mg intravenous dose of sitagliptin to healthy subjects is approximately 198 liters. The fraction of sitagliptin reversibly bound to plasma proteins is low (38%).

Simvastatin

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Rat studies indicate that when radiolabeled simvastatin was administered, simvastatin-derived radioactivity crossed the blood-brain barrier.

Metabolism

Sitagliptin

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination.

Following a [^{14}C]sitagliptin oral dose, approximately 16% of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

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. Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%).

Excretion

Sitagliptin

Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing. The apparent terminal $t_{1/2}$ following a 100 mg oral dose of sitagliptin was approximately 12.4 hours and renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, cyclosporine, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Simvastatin

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose.

Special Populations

Renal Impairment

Sitagliptin

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of sitagliptin (50 mg dose) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (50 to <80 mL/min), moderate (30 to <50 mL/min), and severe (<30 mL/min), as well as patients with ESRD on hemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild or moderate renal impairment were assessed using population pharmacokinetic analyses. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

Compared to normal healthy control subjects, an approximate 1.1- to 1.6-fold increase in plasma AUC of sitagliptin was observed in patients with mild renal impairment. Because increases of this magnitude are not clinically relevant, dosage adjustment in patients with mild renal impairment is not necessary. Plasma AUC levels of sitagliptin were increased approximately 2-fold and 4-fold in patients with moderate renal impairment and in patients with severe renal impairment, including patients with ESRD on hemodialysis, respectively. JUVISYNC should not be used in patients with moderate or severe renal impairment. *[See Dosage and Administration (2.2); Warnings and Precautions (5.4).]*

Hepatic Impairment

Sitagliptin

In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100 mg dose of sitagliptin. These differences are not considered to be clinically meaningful.

There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9).

Body Mass Index (BMI)

Sitagliptin

Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Gender

Sitagliptin

Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Geriatric

Sitagliptin

When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis.

Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin 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. *[see Warnings and Precautions (5.2); Use in Specific Populations (8.5)]*.

Pediatric

Sitagliptin

Studies characterizing the pharmacokinetics of sitagliptin in pediatric patients have not been performed.

Race

Sitagliptin

Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of available pharmacokinetic data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Drug Interactions

Sitagliptin

In Vitro Assessment of Drug Interactions

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways.

Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

In Vivo Assessment of Drug Interactions

Effects of Coadministered Sitagliptin and Simvastatin on Other Drugs

Digoxin: There was an increase in the area under the curve (AUC, 26%) and mean peak drug concentration (C_{max}, 41%) of digoxin with the coadministration of 100 mg sitagliptin and 80 mg simvastatin for 5 days. Patients receiving digoxin and JUVISYNC should be monitored.

Effects of Sitagliptin on Other Drugs

In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

Metformin: Coadministration of multiple twice-daily doses of sitagliptin with metformin, an OCT substrate, did not meaningfully alter the pharmacokinetics of metformin in patients with type 2 diabetes. Therefore, sitagliptin is not an inhibitor of OCT-mediated transport.

Sulfonylureas: Single-dose pharmacokinetics of glyburide, a CYP2C9 substrate, was not meaningfully altered in subjects receiving multiple doses of sitagliptin. Clinically meaningful interactions would not be expected with other sulfonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glyburide, are primarily eliminated by CYP2C9.

Thiazolidinediones: Single-dose pharmacokinetics of rosiglitazone was not meaningfully altered in subjects receiving multiple daily doses of sitagliptin, indicating that sitagliptin is not an inhibitor of CYP2C8-mediated metabolism.

Warfarin: Multiple daily doses of sitagliptin did not meaningfully alter the pharmacokinetics, as assessed by measurement of S(-) or R(+) warfarin enantiomers, or pharmacodynamics (as assessed by measurement of prothrombin INR) of a single dose of warfarin. Because S(-) warfarin is primarily metabolized by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.

Oral Contraceptives: Coadministration with sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl estradiol.

Effects of Other Drugs on Sitagliptin

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by coadministered medications.

Metformin: Coadministration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of cyclosporine increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of Simvastatin on Other Drugs

CYP3A4 Inhibitors: 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.

Effects of Other Drugs on Simvastatin

Cyclosporine: 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.

CYP3A4 Inhibitors: The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy *[see Warnings and Precautions (5.2); Drug Interactions (7.1)]*.

Table 6
Effect of Coadministered Drugs or Grapefruit Juice on Simvastatin Systemic Exposure

Coadministered Drug or Grapefruit Juice	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Simvastatin	Geometric Mean Ratio (Ratio* with / without coadministered drug) No Effect = 1.00		
				AUC	C_{max}
Contraindicated with JUVISYNC *[see Contraindications (4); Warnings and Precautions (5.2)]*					
Telithromycin[†]	200 mg QD for 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 for 4 days	80 mg	simvastatin acid[‡] simvastatin		13.1 13.1
Posaconazole	100 mg (oral suspension) QD for 13 days 200 mg (oral suspension) QD for 13 days	40 mg 40 mg	simvastatin acid simvastatin simvastatin acid simvastatin	7.3 10.3 8.5 10.6	9.2 9.4 9.5 11.4
Gemfibrozil	600 mg BID for 3 days	40 mg	simvastatin acid simvastatin	2.85 1.35	2.18 0.91
Avoid >1 quart of grapefruit juice *[see Warnings and Precautions 5.2)]*					
Grapefruit Juice[§] (high dose)	200 mL of double-strength TID[¶]	60 mg single dose	simvastatin acid simvastatin	7 16	
Grapefruit 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 >100 mg/10 mg JUVISYNC, based on clinical and/or postmarketing experience *[see Warnings and Precautions (5.2)]*					
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
Diltiazem	120 mg BID for 10 days	80 mg on Day 10	simvastatin acid simvastatin	2.69 3.10	2.69 2.88
Diltiazem	120 mg BID for 14 days	20 mg on Day 14	simvastatin	4.6	3.6
Avoid taking with >100 mg/20 mg JUVISYNC, based on clinical and/or postmarketing experience *[see Warnings and Precautions (5.2)]*					
Amlodipine	10 mg QD for 10 days	80 mg on Day 10	simvastatin acid simvastatin	1.58 1.77	1.56 1.47
Ranolazine SR	1000 mg BID for 7 days	80 mg on Day 1 and Days 6-9	simvastatin acid simvastatin	2.26 1.86	2.28 1.75
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	Simvastatin acid Simvastatin	1.75 1.76	1.72 1.79
No dosing adjustments required for the following:					
Fenofibrate	160 mg QD for 14 days	80 mg QD on Days 8-14	simvastatin acid simvastatin	0.64 0.89	0.89 0.83
Niacin extended-release[Þ]	2 g single dose	20 mg single dose	simvastatin acid simvastatin	1.6 1.4	1.84 1.08
Propranolol	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·eq/mL

[*] Results based on a chemical assay except results with propranolol as indicated.
[†] Results could be representative of the following CYP3A4 inhibitors: ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone.
[‡] Simvastatin acid refers to the β-hydroxyacid of simvastatin.
[§] The effect of amounts of grapefruit juice between those used in these two studies on simvastatin pharmacokinetics has not been studied.
[¶] Double-strength: 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-strength: 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.
[Þ] Chinese patients have an increased risk for myopathy with simvastatin coadministered with lipid-modifying doses (≥ 1 gram/day niacin) of niacin-containing products, and the risk is dose-related *[see Warnings and Precautions (5.2); Drug Interactions (7.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sitagliptin

A two-year carcinogenicity study was conducted in male and female rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exposures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/day based on AUC comparisons. Liver tumors were not observed at 150 mg/kg, approximately 20 times the human exposure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given oral doses of sitagliptin of 50, 125, 250, and 500 mg/kg/day. There was no increase in the incidence of tumors in any organ up to 500 mg/kg, approximately 70 times human exposure at the MRHD. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an *in vitro* cytogenetics assay in CHO, an *in vitro* rat hepatocyte DNA alkaline elution assay, and an *in vivo* micronucleus assay.

In rat fertility studies with oral gavage doses of 125, 250, and 1000 mg/kg, males were treated for 4 weeks prior to mating, during mating, up to scheduled termination (approximately 8 weeks total) and females were treated 2 weeks prior to mating through gestation day 7. No adverse effect on fertility was observed at 125 mg/kg (approximately 12 times human exposure at the MRHD of 100 mg/day based on AUC comparisons). At higher doses, nondose-related increased resorptions in females were observed (approximately 25 and 100 times human exposure at the MRHD based on AUC comparison).

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 2, 8, and 16 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after a 40 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 approximately 2 times higher than humans given 40 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 22 times higher levels of simvastatin than in humans given 40 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 14 and 30 times (males) and 44 and 50 times (females) the mean human plasma drug exposure after a 40 milligram 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 (8 times the maximum human exposure level, based on AUC, in patients receiving 40 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 44 times higher than those in humans taking 40 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, (approximately 4 times the human exposure, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

13.2 Animal Toxicology and/or Pharmacology

Simvastatin

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 24 times higher than the mean plasma drug level in humans taking 40 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 28 times higher than the mean plasma drug levels in humans taking 40 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 (44 and 50 times the human AUC at 40 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (38 times) and at two years at 50 mg/kg/day (10 times).

14 CLINICAL STUDIES

14.1 Sitagliptin Clinical Studies

There were approximately 5200 patients with type 2 diabetes randomized in nine double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of sitagliptin on glycemic control. In a pooled analysis of seven of these studies, the ethnic/racial distribution was approximately 59% white, 20% Hispanic, 10% Asian, 6% black, and 6% other groups. Patients had an overall mean age of approximately 55 years (range 18 to 87 years). In addition, an active (glipizide)-controlled study of 52 weeks duration was conducted in 1172 patients with type 2 diabetes who had inadequate glycemic control on metformin.

Reference ID: 3025884

In patients with type 2 diabetes, treatment with sitagliptin produced clinically significant improvements in hemoglobin A1C, fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG) compared to placebo.

Monotherapy

A total of 1262 patients with type 2 diabetes participated in two double-blind, placebo-controlled studies, one of 18-week and another of 24-week duration, to evaluate the efficacy and safety of sitagliptin monotherapy. In both monotherapy studies, patients currently on an antihyperglycemic agent discontinued the agent, and underwent a diet, exercise, and drug washout period of about 7 weeks. Patients with inadequate glycemic control (A1C 7% to 10%) after the washout period were randomized after completing a 2-week single-blind placebo run-in period; patients not currently on antihyperglycemic agents (off therapy for at least 8 weeks) with inadequate glycemic control (A1C 7% to 10%) were randomized after completing the 2-week single-blind placebo run-in period. In the 18-week study, 521 patients were randomized to placebo, sitagliptin 100 mg, or sitagliptin 200 mg, and in the 24-week study 741 patients were randomized to placebo, sitagliptin 100 mg, or sitagliptin 200 mg. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue, added on to placebo or sitagliptin.

Treatment with sitagliptin at 100 mg daily provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo (Table 7). In the 18-week study, 9% of patients receiving sitagliptin 100 mg and 17% who received placebo required rescue therapy. In the 24-week study, 9% of patients receiving sitagliptin 100 mg and 21% of patients receiving placebo required rescue therapy. The improvement in A1C compared to placebo was not affected by gender, age, race, prior antihyperglycemic therapy, or baseline BMI. As is typical for trials of agents to treat type 2 diabetes, the mean reduction in A1C with sitagliptin appears to be related to the degree of A1C elevation at baseline. In these 18- and 24-week studies, among patients who were not on an antihyperglycemic agent at study entry, the reductions from baseline in A1C were -0.7% and -0.8%, respectively, for those given sitagliptin, and -0.1% and -0.2%, respectively, for those given placebo. Overall, the 200 mg daily dose did not provide greater glycemic efficacy than the 100 mg daily dose. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.

Table 7
Glycemic Parameters in 18- and 24-Week Placebo-Controlled Studies of Sitagliptin in Patients with Type 2 Diabetes[†]

	18-Week Study		24-Week Study	
	Sitagliptin 100 mg	**Placebo**	**Sitagliptin 100 mg**	**Placebo**
A1C (%)	**N = 193**	**N = 103**	**N = 229**	**N = 244**
Baseline (mean)	8.0	8.1	8.0	8.0
Change from baseline (adjusted mean[‡])	-0.5	0.1	-0.6	0.2
Difference from placebo (adjusted mean[‡]) (95% CI)	-0.6[§] (-0.8, -0.4)		-0.8[§] (-1.0, -0.6)	
Patients (%) achieving A1C <7%	69 (36%)	16 (16%)	93 (41%)	41 (17%)
FPG (mg/dL)	**N = 201**	**N = 107**	**N = 234**	**N = 247**
Baseline (mean)	180	184	170	176
Change from baseline (adjusted mean[‡])	-13	7	-12	5
Difference from placebo (adjusted mean[‡]) (95% CI)	-20[§] (-31, -9)		-17[§] (-24, -10)	
2-hour PPG (mg/dL)	‖	‖	**N = 201**	**N = 204**
Baseline (mean)			257	271
Change from baseline (adjusted mean[‡])			-49	-2
Difference from placebo (adjusted mean[‡]) (95% CI)			-47[§] (-59, -34)	

[†] Intent-to-treat population using last observation on study prior to metformin rescue therapy.
[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
[§] p<0.001 compared to placebo.
‖ Data not available.

Add-on Combination Therapy with Metformin

A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin. Patients already on metformin (N=431) at a dose of at least 1500 mg per day were randomized after completing a 2-week single-blind placebo run-in period. Patients on metformin and another antihyperglycemic agent (N=229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, N=41) were randomized after a run-in period of approximately 10 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Patients with inadequate glycemic control (A1C 7% to 10%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with metformin, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin (Table 8). Rescue glycemic therapy was used in 5% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups.

Table 8
Glycemic Parameters at Final Visit (24-Week Study)
for Sitagliptin in Add-on Combination Therapy with Metformin†

	Sitagliptin 100 mg + Metformin	Placebo + Metformin
A1C (%)	**N = 453**	**N = 224**
Baseline (mean)	8.0	8.0
Change from baseline (adjusted mean‡)	-0.7	-0.0
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-0.7§ (-0.8, -0.5)	
Patients (%) achieving A1C <7%	213 (47%)	41 (18%)
FPG (mg/dL)	**N = 454**	**N = 226**
Baseline (mean)	170	174
Change from baseline (adjusted mean‡)	-17	9
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-25§ (-31, -20)	
2-hour PPG (mg/dL)	**N = 387**	**N = 182**
Baseline (mean)	275	272
Change from baseline (adjusted mean‡)	-62	-11
Difference from placebo + metformin (adjusted mean‡) (95% CI)	-51§ (-61, -41)	

† Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.
‡ Least squares means adjusted for prior antihyperglycemic therapy and baseline value.
§ p<0.001 compared to placebo + metformin.

Initial Combination Therapy with Metformin

A total of 1091 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind, placebo-controlled factorial study designed to assess the efficacy of sitagliptin as initial therapy in combination with metformin. Patients on an antihyperglycemic agent (N=541) discontinued the agent, and underwent a diet, exercise, and drug washout period of up to 12 weeks duration. After the washout period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized after completing a 2-week single-blind placebo run-in period. Patients not on antihyperglycemic agents at study entry (N=550) with inadequate glycemic control (A1C 7.5% to 11%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive initial therapy with placebo, 100 mg of sitagliptin once daily, 500 mg or 1000 mg of metformin twice daily, or 50 mg of sitagliptin twice daily in combination with 500 mg or 1000 mg of metformin twice daily. Patients who failed to meet specific glycemic goals during the study were treated with glyburide (glibenclamide) rescue.

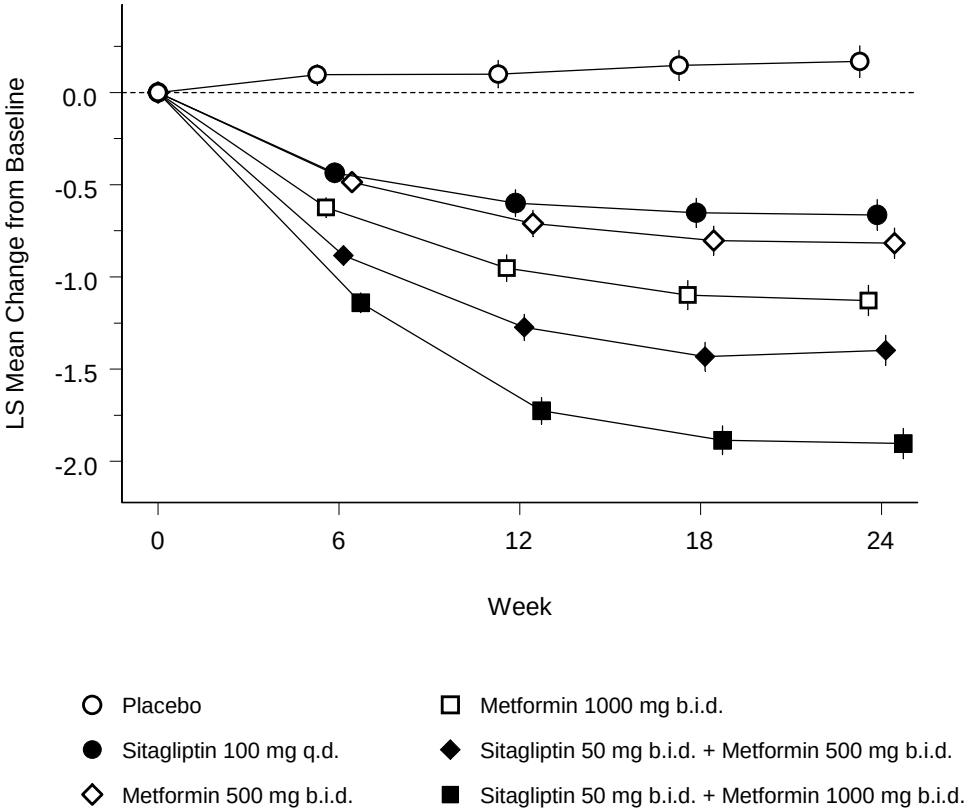
Initial therapy with the combination of sitagliptin and metformin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo, to metformin alone, and to sitagliptin alone (Table 9, Figure 1). Mean reductions from baseline in A1C were generally greater for patients with higher baseline A1C values. For patients not on an antihyperglycemic agent at study entry, mean reductions from baseline in A1C were: sitagliptin 100 mg once daily, -1.1%; metformin 500 mg bid, -1.1%; metformin 1000 mg bid, -1.2%; sitagliptin 50 mg bid with metformin 500 mg bid, -1.6%; sitagliptin 50 mg bid with metformin 1000 mg bid, -1.9%; and for patients receiving placebo, -0.2%. The decrease in body weight in the groups given sitagliptin in combination with metformin was similar to that in the groups given metformin alone or placebo.

Table 9
Glycemic Parameters at Final Visit (24-Week Study)
for Sitagliptin and Metformin, Alone and in Combination as Initial Therapy†

	Placebo	Sitagliptin 100 mg QD	Metformin 500 mg bid	Metformin 1000 mg bid	Sitagliptin 50 mg bid + Metformin 500 mg bid	Sitagliptin 50 mg bid + Metformin 1000 mg bid
A1C (%)	**N = 165**	**N = 175**	**N = 178**	**N = 177**	**N = 183**	**N = 178**
Baseline (mean)	8.7	8.9	8.9	8.7	8.8	8.8
Change from baseline (adjusted mean‡)	0.2	-0.7	-0.8	-1.1	-1.4	-1.9
Difference from placebo (adjusted mean‡) (95% CI)		-0.8§ (-1.1, -0.6)	-1.0§ (-1.2, -0.8)	-1.3§ (-1.5, -1.1)	-1.6§ (-1.8, -1.3)	-2.1§ (-2.3, -1.8)
Patients (%) achieving A1C <7%	15 (9%)	35 (20%)	41 (23%)	68 (38%)	79 (43%)	118 (66%)
% Patients receiving rescue medication	32	21	17	12	8	2
FPG (mg/dL)	**N = 169**	**N = 178**	**N = 179**	**N = 179**	**N = 183**	**N = 180**
Baseline (mean)	196	201	205	197	204	197
Change from baseline (adjusted mean‡)	6	-17	-27	-29	-47	-64
Difference from placebo (adjusted mean‡) (95% CI)		-23§ (-33, -14)	-33§ (-43, -24)	-35§ (-45, -26)	-53§ (-62, -43)	-70§ (-79, -60)
2-hour PPG (mg/dL)	**N = 129**	**N = 136**	**N = 141**	**N = 138**	**N = 147**	**N = 152**
Baseline (mean)	277	285	293	283	292	287
Change from baseline (adjusted mean‡)	0	-52	-53	-78	-93	-117
Difference from placebo (adjusted mean‡) (95% CI)		-52§ (-67, -37)	-54§ (-69, -39)	-78§ (-93, -63)	-93§ (-107, -78)	-117§ (-131, -102)

† Intent-to-treat population using last observation on study prior to glyburide (glibenclamide) rescue therapy.
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§ p<0.001 compared to placebo.

Figure 1: Mean Change from Baseline for A1C (%) over 24 Weeks with Sitagliptin and Metformin, Alone and in Combination as Initial Therapy in Patients with Type 2 Diabetes†



†All Patients Treated Population; least squares means adjusted for prior antihyperglycemic therapy and baseline value.

In addition, this study included patients (N=117) with more severe hyperglycemia (A1C >11% or blood glucose >280 mg/dL) who were treated with twice daily open-label sitagliptin 50 mg and metformin 1000 mg. In this group of patients, the mean baseline A1C value was 11.2%, mean FPG was 314 mg/dL, and mean 2-hour PPG was 441 mg/dL. After 24 weeks, mean decreases from baseline of -2.9% for A1C, -127 mg/dL for FPG, and -208 mg/dL for 2-hour PPG were observed.

Initial combination therapy or maintenance of combination therapy may not be appropriate for all patients. These management options are left to the discretion of the health care provider.

Active-Controlled Study vs Glipizide in Combination with Metformin

The efficacy of sitagliptin was evaluated in a 52-week, double-blind, glipizide-controlled noninferiority trial in patients with type 2 diabetes. Patients not on treatment or on other antihyperglycemic agents entered a run-in treatment period of up to 12 weeks duration with metformin monotherapy (dose of ≥1500 mg per day) which included washout of medications other than metformin, if applicable. After the run-in period, those with inadequate glycemic control (A1C 6.5% to 10%) were randomized 1:1 to the addition of sitagliptin 100 mg once daily or glipizide for 52 weeks. Patients receiving glipizide were given an initial dosage of 5 mg/day and then electively titrated over the next 18 weeks to a maximum dosage of 20 mg/day as needed to optimize glycemic control. Thereafter, the glipizide dose was to be kept constant, except for down-titration to prevent hypoglycemia. The mean dose of glipizide after the titration period was 10 mg.

After 52 weeks, sitagliptin and glipizide had similar mean reductions from baseline in A1C in the intent-to-treat analysis (Table 10). These results were consistent with the per protocol analysis (Figure 2).

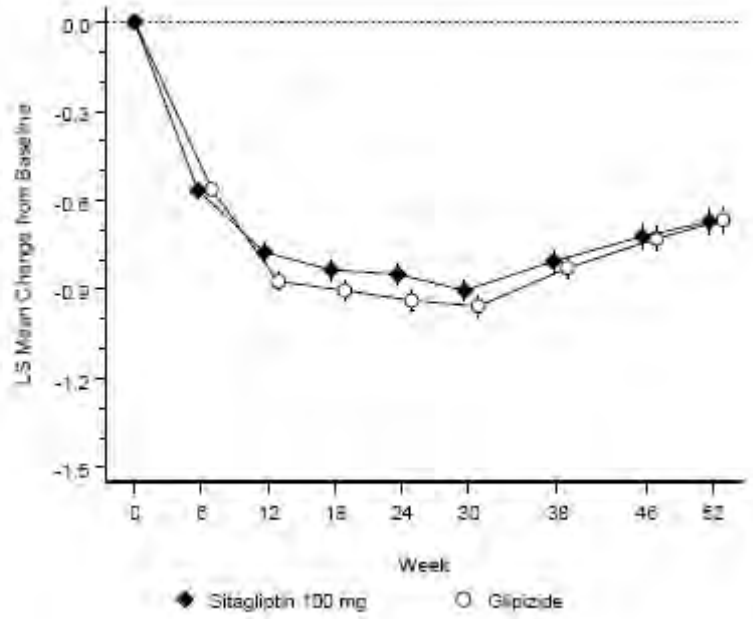
A conclusion in favor of the non-inferiority of sitagliptin to glipizide may be limited to patients with baseline A1C comparable to those included in the study (over 70% of patients had baseline A1C <8% and over 90% had A1C <9%).

Table 10
Glycemic Parameters in a 52-Week Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin (Intent-to-Treat Population)†

	Sitagliptin 100 mg	Glipizide
A1C (%)	**N = 576**	**N = 559**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean‡)	-0.5	-0.6
FPG (mg/dL)	**N = 583**	**N = 568**
Baseline (mean)	166	164
Change from baseline (adjusted mean‡)	-8	-8

† The intent-to-treat analysis used the patients' last observation in the study prior to discontinuation.
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline A1C value.

Figure 2: Mean Change from Baseline for A1C (%) Over 52 Weeks in a Study Comparing Sitagliptin to Glipizide as Add-On Therapy in Patients Inadequately Controlled on Metformin (Per Protocol Population)†



† The per protocol population (mean baseline A1C of 7.5%) included patients without major protocol violations who had observations at baseline and at Week 52.

The incidence of hypoglycemia in the sitagliptin group (4.9%) was significantly (p<0.001) lower than that in the glipizide group (32.0%). Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 kg vs +1.1 kg).

Add-on Combination Therapy with Pioglitazone

A total of 353 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with pioglitazone. Patients on any oral antihyperglycemic agent in monotherapy (N=212) or on a PPARγ agent in combination therapy (N=106) or not on an antihyperglycemic agent (off therapy for at least 8 weeks, N=34) were switched to monotherapy with pioglitazone (at a dose of 30-45 mg per day), and completed a run-in period of approximately 12 weeks in duration. After the run-in period on pioglitazone monotherapy, patients with inadequate glycemic control (A1C 7% to 10%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with metformin rescue. Glycemic endpoints measured were A1C and fasting glucose.

In combination with pioglitazone, sitagliptin provided significant improvements in A1C and FPG compared to placebo with pioglitazone (Table 11). Rescue therapy was used in 7% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

Table 11
Glycemic Parameters at Final Visit (24-Week Study)
for Sitagliptin in Add-on Combination Therapy with Pioglitazone[†]

	Sitagliptin 100 mg + Pioglitazone	**Placebo + Pioglitazone**
A1C (%)	**N = 163**	**N = 174**
Baseline (mean)	8.1	8.0
Change from baseline (adjusted mean[‡])	-0.9	-0.2
Difference from placebo + pioglitazone (adjusted mean[‡]) (95% CI)	-0.7[§] (-0.9, -0.5)	
Patients (%) achieving A1C <7%	74 (45%)	40 (23%)
FPG (mg/dL)	**N = 163**	**N = 174**
Baseline (mean)	168	166
Change from baseline (adjusted mean[‡])	-17	1
Difference from placebo + pioglitazone (adjusted mean[‡]) (95% CI)	-18[§] (-24, -11)	

[†] Intent-to-treat population using last observation on study prior to metformin rescue therapy.
[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
[§] p<0.001 compared to placebo + pioglitazone.

Initial Combination Therapy with Pioglitazone

A total of 520 patients with type 2 diabetes and inadequate glycemic control on diet and exercise participated in a 24-week, randomized, double-blind study designed to assess the efficacy of sitagliptin as initial therapy in combination with pioglitazone. Patients not on antihyperglycemic agents at study entry (<4 weeks cumulative therapy over the past 2 years, and with no treatment over the prior 4 months) with inadequate glycemic control (A1C 8% to 12%) immediately entered the 2-week single-blind placebo run-in period and then were randomized. Approximately equal numbers of patients were randomized to receive initial therapy with 100 mg of sitagliptin in combination with 30 mg of pioglitazone once daily or 30 mg of pioglitazone once daily as monotherapy. There was no glycemic rescue therapy in this study.

Initial therapy with the combination of sitagliptin and pioglitazone provided significant improvements in A1C, FPG, and 2-hour PPG compared to pioglitazone monotherapy (Table 12). The improvement in A1C was generally consistent across subgroups defined by gender, age, race, baseline BMI, baseline A1C, or duration of disease. In this study, patients treated with sitagliptin in combination with pioglitazone had a mean increase in body weight of 1.1 kg compared to pioglitazone alone (3.0 kg vs. 1.9 kg).

Table 12
Glycemic Parameters at Final Visit (24-Week Study)
for Sitagliptin in Combination with Pioglitazone as Initial Therapy†

	Sitagliptin 100 mg + Pioglitazone	Pioglitazone
A1C (%)	**N = 251**	**N = 246**
Baseline (mean)	9.5	9.4
Change from baseline (adjusted mean‡)	-2.4	-1.5
Difference from pioglitazone (adjusted mean‡) (95% CI)	-0.9§ (-1.1, -0.7)	
Patients (%) achieving A1C <7%	151 (60%)	68 (28%)
FPG (mg/dL)	**N = 256**	**N = 253**
Baseline (mean)	203	201
Change from baseline (adjusted mean‡)	-63	-40
Difference from pioglitazone (adjusted mean‡) (95% CI)	-23§ (-30, -15)	
2-hour PPG (mg/dL)	**N = 216**	**N = 211**
Baseline (mean)	283	284
Change from baseline (adjusted mean‡)	-114	-69
Difference from pioglitazone (adjusted mean‡) (95% CI)	-45§ (-57, -32)	

† Intent-to-treat population using last observation on study.
‡ Least squares means adjusted for baseline value.
§ p<0.001 compared to placebo + pioglitazone.

Add-on Combination Therapy with Metformin and Rosiglitazone

A total of 278 patients with type 2 diabetes participated in a 54-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin and rosiglitazone. Patients on dual therapy with metformin ≥1500 mg/day and rosiglitazone ≥4 mg/day or with metformin ≥1500 mg/day and pioglitazone ≥30 mg/day (switched to rosiglitazone ≥4 mg/day) entered a dose-stable run-in period of 6 weeks. Patients on other dual therapy were switched to metformin ≥1500 mg/day and rosiglitazone ≥4 mg/day in a dose titration/stabilization run-in period of up to 20 weeks in duration. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized 2:1 to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the study were treated with glipizide (or other sulfonylurea) rescue. The primary time point for evaluation of glycemic parameters was Week 18.

In combination with metformin and rosiglitazone, sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin and rosiglitazone (Table 13) at Week 18. At Week 54, mean reduction in A1C was -1.0% for patients treated with sitagliptin and -0.3% for patients treated with placebo in an analysis based on the intent-to-treat population. Rescue therapy was used in 18% of patients treated with sitagliptin 100 mg and 40% of patients treated with placebo. There was no significant difference between sitagliptin and placebo in body weight change.

Table 13
Glycemic Parameters at Week 18
for Sitagliptin in Add-on Combination Therapy with Metformin and Rosiglitazone[†]

	Sitagliptin 100 mg + Metformin + Rosiglitazone	Placebo + Metformin + Rosiglitazone
A1C (%)	**N = 176**	**N = 93**
Baseline (mean)	8.8	8.7
Change from baseline (adjusted mean[‡])	-1.0	-0.4
Difference from placebo + rosiglitazone + metformin (adjusted mean[‡]) (95% CI)	-0.7[§] (-0.9, -0.4)	
Patients (%) achieving A1C <7%	39 (22%)	9 (10%)
FPG (mg/dL)	**N = 179**	**N = 94**
Baseline (mean)	181	182
Change from baseline (adjusted mean[‡])	-30	-11
Difference from placebo + rosiglitazone + metformin (adjusted mean[‡]) (95% CI)	-18[§] (-26, -10)	
2-hour PPG (mg/dL)	**N = 152**	**N = 80**
Baseline (mean)	256	248
Change from baseline (adjusted mean[‡])	-59	-21
Difference from placebo + rosiglitazone + metformin (adjusted mean[‡]) (95% CI)	-39[§] (-51, -26)	

[†] Intent-to-treat population using last observation on study prior to glipizide (or other sulfonylurea) rescue therapy.
[‡] Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
[§] p<0.001 compared to placebo + metformin + rosiglitazone.

Add-on Combination Therapy with Glimepiride, with or without Metformin

A total of 441 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with glimepiride, with or without metformin. Patients entered a run-in treatment period on glimepiride (≥4 mg per day) alone or glimepiride in combination with metformin (≥1500 mg per day). After a dose-titration and dose-stable run-in period of up to 16 weeks and a 2-week placebo run-in period, patients with inadequate glycemic control (A1C 7.5% to 10.5%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue.

In combination with glimepiride, with or without metformin, sitagliptin provided significant improvements in A1C and FPG compared to placebo (Table 14). In the entire study population (patients on sitagliptin in combination with glimepiride and patients on sitagliptin in combination with glimepiride and metformin), a mean reduction from baseline relative to placebo in A1C of -0.7% and in FPG of -20 mg/dL was seen. Rescue therapy was used in 12% of patients treated with sitagliptin 100 mg and 27% of patients treated with placebo. In this study, patients treated with sitagliptin had a mean increase in body weight of 1.1 kg vs. placebo (+0.8 kg vs. -0.4 kg). In addition, there was an increased rate of hypoglycemia. *[See Warnings and Precautions (5.5); Adverse Reactions (6.1).]*

Table 14
Glycemic Parameters at Final Visit (24-Week Study)
for Sitagliptin as Add-On Combination Therapy with Glimepiride, with or without Metformin†

	Sitagliptin 100 mg + Glimepiride	Placebo + Glimepiride	Sitagliptin 100 mg + Glimepiride + Metformin	Placebo + Glimepiride + Metformin
A1C (%)	**N = 102**	**N = 103**	**N = 115**	**N = 105**
Baseline (mean)	8.4	8.5	8.3	8.3
Change from baseline (adjusted mean‡)	-0.3	0.3	-0.6	0.3
Difference from placebo (adjusted mean‡) (95% CI)	-0.6§ (-0.8, -0.3)		-0.9§ (-1.1, -0.7)	
Patients (%) achieving A1C <7%	11 (11%)	9 (9%)	26 (23%)	1 (1%)
FPG (mg/dL)	**N = 104**	**N = 104**	**N = 115**	**N = 109**
Baseline (mean)	183	185	179	179
Change from baseline (adjusted mean‡)	-1	18	-8	13
Difference from placebo (adjusted mean‡) (95% CI)	-19‖ (-32, -7)		-21§ (-32, -10)	

† Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy.
‡ Least squares means adjusted for prior antihyperglycemic therapy status and baseline value.
§ p<0.001 compared to placebo.
‖ p<0.01 compared to placebo.

Add-on Combination Therapy with Insulin (with or without Metformin)

A total of 641 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin as add-on to insulin therapy (with or without metformin). The racial distribution in this study was approximately 70% white, 18% Asian, 7% black, and 5% other groups. Approximately 14% of the patients in this study were Hispanic. Patients entered a 2-week, single-blind run-in treatment period on pre-mixed, long-acting, or intermediate-acting insulin, with or without metformin (≥1500 mg per day). Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a pre-mixed insulin. After the run-in period, patients with inadequate glycemic control (A1C 7.5% to 11%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients were on a stable dose of insulin prior to enrollment with no changes in insulin dose permitted during the run-in period. Patients who failed to meet specific glycemic goals during the double-blind treatment period were to have uptitration of the background insulin dose as rescue therapy.

The median daily insulin dose at baseline was 42 units in the patients treated with sitagliptin and 45 units in the placebo-treated patients. The median change from baseline in daily dose of insulin was zero for both groups at the end of the study. In combination with insulin (with or without metformin), sitagliptin provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo (Table 15). Both treatment groups had an adjusted mean increase in body weight of 0.1 kg from baseline to Week 24. There was an increased rate of hypoglycemia in patients treated with sitagliptin. *[See Warnings and Precautions (5.5); Adverse Reactions (6.1).]*

Table 15
Glycemic Parameters at Final Visit (24-Week Study)
for Sitagliptin as Add-on Combination Therapy with Insulin[†]

	Sitagliptin 100 mg + Insulin (+/- Metformin)	Placebo + Insulin (+/- Metformin)
A1C (%)	**N = 305**	**N = 312**
Baseline (mean)	8.7	8.6
Change from baseline (adjusted mean[‡])	-0.6	-0.1
Difference from placebo (adjusted mean[‡,§]) (95% CI)	-0.6[‖] (-0.7, -0.4)	
Patients (%) achieving A1C <7%	39 (12.8%)	16 (5.1%)
FPG (mg/dL)	**N = 310**	**N = 313**
Baseline (mean)	176	179
Change from baseline (adjusted mean[‡])	-18	-4
Difference from placebo (adjusted mean[‡]) (95% CI)	-15[‖] (-23, -7)	
2-hour PPG (mg/dL)	**N = 240**	**N = 257**
Baseline (mean)	291	292
Change from baseline (adjusted mean[‡])	-31	5
Difference from placebo (adjusted mean[‡]) (95% CI)	-36[‖] (-47, -25)	

[†] Intent-to-treat population using last observation on study prior to rescue therapy.
[‡] Least squares means adjusted for metformin use at the screening visit (yes/no), type of insulin used at the screening visit (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.
[§] Treatment by stratum interaction was not significant (p>0.10) for metformin stratum and for insulin stratum.
[‖] p<0.001 compared to placebo.

14.2 Simvastatin Clinical Studies

Reductions in Risk of CHD Mortality and Cardiovascular Events

In 4S, the effect of therapy with simvastatin on total mortality was assessed in 4444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with standard care, including diet, and either simvastatin 20-40 mg/day (n=2221) or placebo (n=2223) for a median duration of 5.4 years. Over the course of the study, treatment with simvastatin led to mean reductions in total-C, LDL-C and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 8%. Simvastatin significantly reduced the risk of mortality by 30% (p=0.0003, 182 deaths in the simvastatin group vs 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42% (p=0.00001, 111 vs 189 deaths). There was no statistically significant difference between groups in non-cardiovascular mortality. Simvastatin significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial infarction [MI]) by 34% (p<0.00001, 431 vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. Simvastatin significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (p<0.00001, 252 vs 383 patients). Simvastatin significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p=0.033, 75 vs 102 patients). Simvastatin reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. Because there were only 53 female deaths, the effect of simvastatin on mortality in women could not be adequately assessed. However, simvastatin significantly lessened the risk of having major coronary events by 34% (60 vs 91 women with one or more event). The randomization was stratified by angina alone (21% of each treatment group) or a previous MI. Because there were only 57 deaths among the patients with angina alone at baseline, the effect of simvastatin on mortality in this subgroup could not be adequately assessed. However, trends in reduced coronary mortality, major coronary events and revascularization procedures were consistent between this group and the total study

cohort. Additionally, simvastatin resulted in similar decreases in relative risk for total mortality, CHD mortality, and major coronary events in elderly patients (≥65 years), compared with younger patients.

The Heart Protection Study (HPS) was a large, multi-center, placebo-controlled, double-blind study with a mean duration of 5 years conducted in 20,536 patients (10,269 on simvastatin 40 mg and 10,267 on placebo), including 5963 patients with diabetes mellitus (2978 on simvastatin and 2985 on placebo). Patients were allocated to treatment using a covariate adaptive method[2] which took into account the distribution of 10 important baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients had a mean age of 64 years (range 40-80 years), were 97% Caucasian and were at high risk of developing a major coronary event because of existing CHD (65%), diabetes (Type 2, 26%; Type 1, 3%), history of stroke or other cerebrovascular disease (16%), peripheral vessel disease (33%), or hypertension in males ≥65 years (6%). At baseline, 3421 patients (17%) had LDL-C levels below 100 mg/dL, of whom 953 (5%) had LDL-C levels below 80 mg/dL; 7068 patients (34%) had levels between 100 and 130 mg/dL; and 10,047 patients (49%) had levels greater than 130 mg/dL.

The HPS results showed that simvastatin 40 mg/day significantly reduced: total and CHD mortality; non-fatal MI, stroke, and revascularization procedures (coronary and non-coronary) (see Table 16).

Table 16
Summary of Heart Protection Study Results

Endpoint	**Simvastatin** (N=10,269) n (%)[†]	**Placebo** (N=10,267) n (%)[†]	**Risk Reduction (%) (95% CI)**	**p-Value**
Primary				
Mortality	1328 (12.9)	1507 (14.7)	13 (6-19)	p=0.0003
CHD mortality	587 (5.7)	707 (6.9)	18 (8-26)	p=0.0005
Secondary				
Non-fatal MI	357 (3.5)	574 (5.6)	38 (30-46)	p<0.0001
Stroke	444 (4.3)	585 (5.7)	25 (15-34)	p<0.0001
Tertiary				
Coronary revascularization	513 (5)	725 (7.1)	30 (22-38)	p<0.0001
Peripheral and other non-coronary revascularization	450 (4.4)	532 (5.2)	16 (5-26)	p=0.006

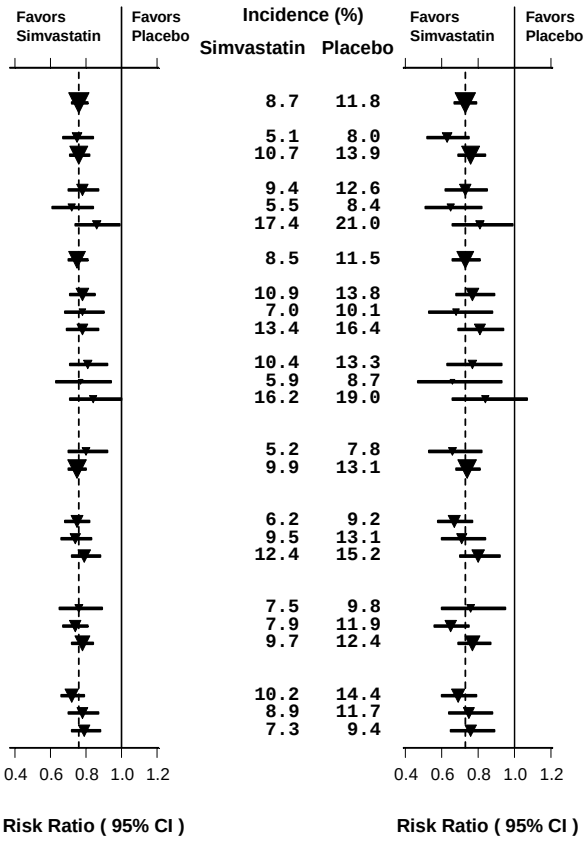
[†] n = number of patients with indicated event

Two composite endpoints were defined in order to have sufficient events to assess relative risk reductions across a range of baseline characteristics (see Figure 3). A composite of major coronary events (MCE) was comprised of CHD mortality and non-fatal MI (analyzed by time-to-first event; 898 patients treated with simvastatin had events and 1212 patients on placebo had events). A composite of major vascular events (MVE) was comprised of MCE, stroke and revascularization procedures including coronary, peripheral and other non-coronary procedures (analyzed by time-to-first event; 2033 patients treated with simvastatin had events and 2585 patients on placebo had events). Significant relative risk reductions were observed for both composite endpoints (27% for MCE and 24% for MVE, p<0.0001). Treatment with simvastatin produced significant relative risk reductions for all components of the composite endpoints. The risk reductions produced by simvastatin in both MCE and MVE were evident and consistent regardless of cardiovascular disease related medical history at study entry (i.e., CHD alone; or peripheral vascular disease, cerebrovascular disease, diabetes or treated hypertension, with or without CHD), gender, age, creatinine levels up to the entry limit of 2.3 mg/dL, baseline levels of LDL-C, HDL-C, apolipoprotein B and A-1, baseline concomitant cardiovascular medications (i.e., aspirin, beta blockers, or calcium channel blockers), smoking status, alcohol intake, or obesity. Diabetic patients showed risk reductions for MCE and MVE (27% and 22%, respectively; p<0.0001) due to simvastatin treatment regardless of baseline A1C levels or obesity with the greatest effects seen for diabetic patients without CHD.

Reference ID: 3025884

Figure 3
The Effects of Treatment with Simvastatin on Major Vascular Events and Major Coronary Events in HPS

Baseline Characteristics	N	Major Vascular Events Incidence (%) Simvastatin	Major Vascular Events Incidence (%) Placebo	Major Coronary Events Incidence (%) Simvastatin	Major Coronary Events Incidence (%) Placebo
All patients	20,536	19.8	25.2	8.7	11.8
Without CHD	7,150	16.1	20.8	5.1	8.0
With CHD	13,386	21.8	27.5	10.7	13.9
Diabetes mellitus	5,963	20.2	25.1	9.4	12.6
Without CHD	3,982	13.8	18.6	5.5	8.4
With CHD	1,981	33.4	37.8	17.4	21.0
Without diabetes mellitus	14,573	19.6	25.2	8.5	11.5
Peripheral vascular disease	6,748	26.4	32.7	10.9	13.8
Without CHD	2,701	24.7	30.5	7.0	10.1
With CHD	4,047	27.6	34.3	13.4	16.4
Cerebrovascular disease	3,280	24.7	29.8	10.4	13.3
Without CHD	1,820	18.7	23.6	5.9	8.7
With CHD	1,460	32.4	37.4	16.2	19.0
Gender					
Female	5,082	14.4	17.7	5.2	7.8
Male	15,454	21.6	27.6	9.9	13.1
Age (years)					
≥ 40 to < 65	9,839	16.9	22.1	6.2	9.2
≥ 65 to < 70	4,891	20.9	27.2	9.5	13.1
≥ 70	5,806	23.6	28.7	12.4	15.2
LDL-cholesterol (mg/dL)					
< 100	3,421	16.4	21.0	7.5	9.8
≥ 100 to < 130	7,068	18.9	24.7	7.9	11.9
≥ 130	10,047	21.6	26.9	9.7	12.4
HDL-cholesterol (mg/dL)					
< 35	7,176	22.6	29.9	10.2	14.4
≥ 35 to < 43	5,666	20.0	25.1	8.9	11.7
≥ 43	7,694	17.0	20.9	7.3	9.4



N = number of patients in each subgroup. The inverted triangles are point estimates of the relative risk, with their 95% confidence intervals represented as a line. The area of a triangle is proportional to the number of patients with MVE or MCE in the subgroup relative to the number with MVE or MCE, respectively, in the entire study population. The vertical solid line represents a relative risk of one. The vertical dashed line represents the point estimate of relative risk in the entire study population.

Modifications of Lipid Profiles

Primary Hyperlipidemia (Fredrickson type lla and llb)

Simvastatin has been shown to be effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of hyperlipidemia and in mixed hyperlipidemia. Maximal to near maximal response is generally achieved within 4-6 weeks and maintained during chronic therapy. Simvastatin consistently and significantly decreased total-C, LDL-C, total-C/HDL-C ratio, and LDL-C/HDL-C ratio; simvastatin also decreased TG and increased HDL-C (see Table 17).

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.

Reference ID: 3025884

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.

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 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 be swallowed whole and never split, crushed or chewed.

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 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. The risk of myopathy, including rhabdomyolysis, occurring with use of JUVISYNC is increased when taking certain types of medication or consuming larger quantities of 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.

Manufactured for:
Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

Manufactured by:

MSD International GmbH
Clonmel, Co. Tipperary,
Ireland

6065500

US Patent No.: 6,699,871

Copyright © 2011 Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**
All rights reserved