Attachment 1: Product information for AusPAR Juvicor/Xelezor/Tesozor Sitagliptin and Simvastatin, Merck, Sharp & Dohme Australia Pty Ltd PM-2011-02796-3-5. This Product Information was approved at the time this AusPAR was published.

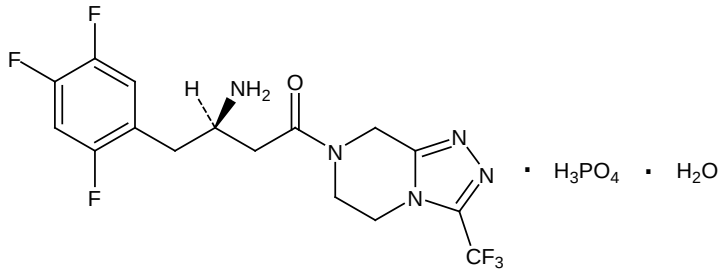
PRODUCT INFORMATION

JUVICOR®
(sitagliptin phosphate monohydrate/simvastatin, MSD)

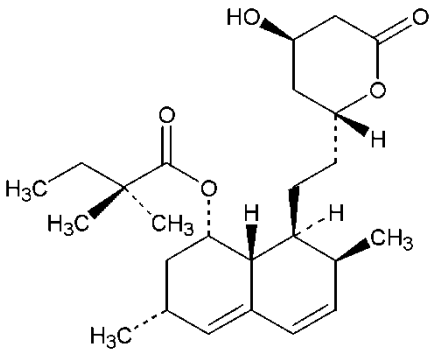
JUVICOR 100/10 mg
JUVICOR 100/20 mg
JUVICOR 100/40 mg

NAME OF THE MEDICINE
JUVICOR tablets contain sitagliptin (as phosphate monohydrate) and simvastatin.

Sitagliptin phosphate monohydrate (CAS no.: 654671-77-9), 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 $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



Simvastatin (CAS no.: 79902-63-9), is described chemically as [1*S*-[1α,3α,7β,8β(2*S**,4*S**),8αβ]]-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 2,2-dimethylbutanoate. The empirical formula is $C_{25}H_{38}O_5$ and the molecular weight is 418.57. The structural formula is:



DESCRIPTION
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. The pH of a saturated water solution of sitagliptin phosphate monohydrate is 4.4. The partition coefficient is 1.8 and the pK_a is 7.7. **Simvastatin** is a white crystalline powder, practically insoluble in water and freely soluble in chloroform, methanol and ethanol. The partition coefficient is >1995. Simvastatin exhibits no acid/base dissociation constants.

JUVICOR is available for oral use as film-coated bilayer tablets containing 128.5 mg of sitagliptin phosphate monohydrate (equivalent to 100 mg of free base), and either 10 mg, 20 mg, or 40 mg of simvastatin. Each bilayer tablet of JUVICOR also contains the following inactive ingredients: anhydrous calcium hydrogen phosphate, microcrystalline cellulose, croscarmellose sodium, sodium stearylfumarate, magnesium stearate, ascorbic acid, citric acid monohydrate, lactose, and pregelatinised maize starch. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, macrogol 3350, purified talc, titanium dioxide, iron oxide red CI77491, iron oxide yellow CI77492, and iron oxide black CI77499. Butylated hydroxyanisole is added as an antioxidant.

PHARMACOLOGY

Pharmacodynamics

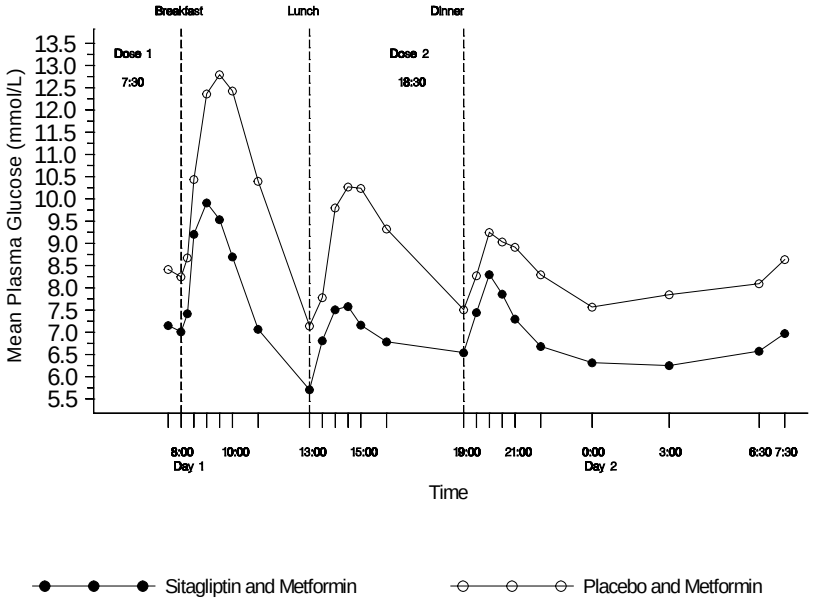
Sitagliptin

Sitagliptin phosphate monohydrate is an orally-active inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes mellitus. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiological 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. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. This mechanism is unlike the mechanism seen with sulfonylureas; sulfonylureas cause insulin release even when glucose levels are low, which can lead to sulfonylurea-induced hypoglycaemia in patients with type 2 diabetes and in normal subjects. Sitagliptin inhibits DPP-4 with nanomolar potency (IC_{50} 18 nM). It does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations.

Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24-hour period, resulting in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal. In a study of patients with type 2 diabetes inadequately controlled on metformin monotherapy, glucose levels monitored throughout the day were significantly lower in patients who received sitagliptin 100 mg per day (50 mg twice daily) in combination with metformin compared with patients who received placebo with metformin (see Figure 1).

Figure 1: 24-hour Plasma Glucose Profile after 4-Week Treatment with Sitagliptin 50 mg BID with Metformin or Placebo with Metformin



In Phase III clinical studies of 18- and 24-week duration, treatment with sitagliptin 100 mg daily in patients with type 2 diabetes significantly improved beta cell function, as assessed by several markers, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. There are no clinical studies that demonstrate that sitagliptin alters the natural history of impaired glucose tolerance or type 2 diabetes mellitus. The durability of efficacy requires further study.

In Phase II studies, sitagliptin 50 mg twice daily provided no additional glycaemic efficacy compared to 100 mg once daily.

In studies with healthy subjects, sitagliptin did not lower blood glucose or cause hypoglycaemia, suggesting that the insulinotropic and glucagon suppressive actions of sitagliptin are glucose dependent (see **PRECAUTIONS**, *Hypoglycaemia in Combination with a Sulfonylurea or with insulin;* **ADVERSE EFFECTS**).

Effects on blood pressure

In a randomised, placebo-controlled crossover study in hypertensive patients on one or more anti-hypertensive medicines (including angiotensin-converting enzyme [ACE] inhibitors, angiotensin-II antagonists, calcium-channel blockers, beta-blockers and diuretics), co-administration with sitagliptin was generally well tolerated. In these patients, sitagliptin had a modest blood pressure lowering effect; 100 mg per day of sitagliptin reduced 24-hour mean ambulatory systolic blood pressure by approximately 2 mmHg, as compared to placebo. Reductions have not been observed in subjects with normal blood pressure.

Cardiac electrophysiology

In a randomised, 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 at 3 hours post-dose was 8.0 msec. This small increase was 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

Simvastatin is a lipid-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolysed to the corresponding β-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme which catalyses an early and rate-limiting step in the biosynthesis of cholesterol. As a result, in clinical studies, simvastatin reduced total plasma cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), and very-low-density lipoprotein cholesterol (VLDL-C) concentrations. In addition, simvastatin increases high-density lipoprotein cholesterol (HDL-C) and reduces plasma triglycerides (TG).

Simvastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from VLDL and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of simvastatin may involve both reduction of VLDL-C concentration and induction of the LDL receptor, leading to reduced production and increased catabolism of LDL-C. Apolipoprotein B (Apo B) also falls substantially during treatment with simvastatin. Since each LDL particle contains one molecule of Apo B, and since little Apo B is found in other lipoproteins, this strongly suggests that simvastatin does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. As a result of these changes, the ratios of total-C to HDL-C and LDL-C to HDL-C are reduced.

Even though simvastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyses the conversion of HMG-CoA to mevalonate is not completely blocked at therapeutic doses, therefore it allows the necessary amounts of mevalonate to be available for biological functions. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway of cholesterol, therapy with simvastatin would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is metabolised readily back to acetyl-CoA, which participates in many biosynthetic processes in the body.

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.

Pharmacokinetics

Absorption

An increase in simvastatin acid mean peak plasma concentration (C_{max}) was observed following co-administration of JUVICOR with a high-fat meal. The pharmacokinetics of sitagliptin were not affected under the same conditions. However, relative to the fasting state, the plasma profile of HMG-CoA reductase inhibitors was not affected when simvastatin was administered immediately before a test (i.e., non-high-fat) meal. JUVICOR

may therefore be administered with or without food, however co-administration with a high-fat meal is not recommended.

The pharmacokinetics of *sitagliptin* have been extensively characterised 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 post-dose. Plasma area under the curve (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, mean plasma 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%.

Peak plasma concentrations of *simvastatin* and β-hydroxyacid were attained within 1.5 and 4-6 hours post-dose, respectively. Based on assays of HMG-CoA inhibition, no substantial deviation from linearity of AUC of inhibitors in the general circulation was observed at doses up to 120 mg. The pharmacokinetic effects of calcium channel blockers on simvastatin and HMG-CoA reductase inhibitors are summarised in Table 1. The data show increases in simvastatin acid exposure (AUC) with calcium channel blockers (see **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*).

Table 1 Effect of Co-administered Calcium Channel Blockers on Simvastatin Systemic Exposure and HMG-CoA Reductase Inhibitory Activity

		Geometric mean ratio (Ratio* with / without co-administered medicine) No Effect = 1.00		
Co-administered medicine and dosing regimen	**Dosing of Simvastatin**		**AUC**	**C_{max}**
Verapamil SR 240 mg QD Days 1-7 then 240 mg BID on Days 8-10	80 mg on Day 10	Simvastatin acid† Simvastatin Active inhibitors Total inhibitors	2.3 2.5 1.8 1.8	2.4 2.1 1.3 1.4
Diltiazem 120 mg BID for 10 Days	80 mg on Day 10	Simvastatin acid† Simvastatin Active inhibitors Total inhibitors	2.7 3.1 2.0 1.7	2.7 2.9 1.6 1.5
Amlodipine 10 mg QD x 10 Days	80 mg on Day 10	Simvastatin acid† Simvastatin Active inhibitors Total inhibitors	1.6 1.8 1.3 1.3	1.6 1.5 0.9 1.0

* Results based on a chemical assay

† Simvastatin acid refers to the β-hydroxyacid of simvastatin

A single dose of 2 g niacin extended-release co-administered with 20 mg simvastatin increased the AUC and C_{max} of simvastatin acid by approximately 60% and 84%, respectively, compared to administration of 20 mg simvastatin alone. In this study, the effect of simvastatin on niacin pharmacokinetics was not measured.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase

inhibitory activity and increase the risk of myopathy (see **PRECAUTIONS**, Myopathy/Rhabdomyolysis; **INTERACTIONS WITH OTHER MEDICINES**).

Distribution

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

Both *simvastatin* and β-hydroxyacid are bound to human plasma proteins (95%).

Metabolism

Approximately 79% of *sitagliptin* is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Following a ^{14}C -labelled 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.

The major metabolites of *simvastatin* present in human plasma are β-hydroxyacid and four additional active metabolites. Simvastatin and other HMG-CoA reductase inhibitors are metabolised by CYP 3A4 (see **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*). Although the mechanism is not fully understood, cyclosporin has been shown to increase the AUC of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4. Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of simvastatin to the general circulation is low. The availability of β-hydroxyacid to the systemic circulation following an oral dose of simvastatin was estimated using an I.V. reference dose of β-hydroxyacid; the value was found to be less than 5% of the dose.

Excretion

Following administration of an oral ^{14}C -labelled *sitagliptin* dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in faeces (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, cyclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin.

Following a 100 mg oral dose of ^{14}C-labelled *simvastatin* in man, 13% of the radioactivity was recovered in urine and 60% in faeces. The latter represents absorbed simvastatin equivalents excreted in bile as well as unabsorbed simvastatin. Less than 0.5% of the dose was recovered in urine as HMG-CoA reductase inhibitors. In plasma, the inhibitors account for 14% and 28% (active and total inhibitors) of the AUC of total radioactivity, indicating that the majority of chemical species present were inactive or weak inhibitors. Following an intravenous injection of the β-hydroxyacid metabolite, its half-life averaged 1.9 hours.

CLINICAL TRIALS

Sitagliptin

Results from long-term studies of sitagliptin on overall morbidity and mortality outcomes are not available.

There were 2,757 patients with type 2 diabetes randomised in five double-blind, placebo-controlled Phase III clinical studies conducted to evaluate the effects of sitagliptin on glycaemic control as monotherapy and in combination with metformin, pioglitazone, glimepiride, and glimepiride+metformin. Co-morbid diseases were common in the patients studied: 58% had hypertension, 54% had dyslipidaemia, and more than 50% were obese (BMI ≥30 kg/m2). The majority of patients (51.6% to 65.8%) met National Cholesterol Education Program (NCEP) criteria for metabolic syndrome. In these studies, the mean age of patients was 55.0 years, and 62% of patients were white, 18% were Hispanic, 6% were black, 9% were Asian, and 4% were of other racial groups. The studies that support registration in general used the reduction in haemoglobin A_{1c} (HbA_{1c}) as the primary outcome variable. Pre-specified secondary endpoints included fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG).

An active (glipizide)-controlled study of 52-weeks duration was conducted in 1,172 patients with type 2 diabetes who had inadequate glycaemic control on metformin. In patients with type 2 diabetes, treatment with sitagliptin produced statistically significant improvements in HbA_{1c}. Clinically significant improvements in HbA_{1c} were maintained for 52 weeks. Treatment with sitagliptin showed suggestions of improvement in measures of beta cell function (see **PHARMACOLOGY**, *Pharmacodynamics*).

Add-on Therapy to Metformin

A total of 701 patients with type 2 diabetes with inadequate glycaemic control on metformin alone participated in a 24-week, randomised, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin (Hb A_{1c} 7% to 10%). All patients were started on metformin monotherapy and the dose increased to at least 1,500 mg per day. Patients were randomised to the addition of either 100 mg of sitagliptin or placebo, administered once daily.

Table 2 Glycaemic Parameters and Body Weight at Final Visit (24-Week Study) for Sitagliptin in Combination with Metformin† - Primary (HbA_{1c}) and Secondary Outcomes

	Sitagliptin 100 mg + Metformin	Placebo + Metformin
HbA_{1c} (%)	**N = 453**	**N = 224**
Baseline (mean)	7.96	8.03
Change from baseline (adjusted mean‡)	-0.67	-0.02
Difference from placebo + metformin	-0.65§	
Patients (%) achieving HbA_{1c} <7%	213 (47.0)	41 (18.3)
FPG (mmol/L)	**N = 454**	**N = 226**
Baseline (mean)	9.44	9.63
Change from baseline (adjusted mean‡)	-0.94	0.47
Difference from placebo + metformin	-1.41§	
2-hour PPG (mmol/L)	**N = 387**	**N = 182**
Baseline (mean)	15.24	15.12
Change from baseline (adjusted mean‡)	-3.44	-0.63
Difference from placebo + metformin	-2.81§	
Body Weight (kg)%	**N = 399**	**N = 169**
Baseline (mean)	86.9	87.6
Change from baseline (adjusted mean‡)	-0.7	-0.6
Difference from placebo + metformin	-0.1¶	

† All Patients Treated Population (an intention-to-treat analysis).

‡ Least squares means adjusted for prior antihyperglycaemic therapy and baseline value.

§ p<0.001 compared to placebo + metformin.

% All Patients as Treated (APaT) population, excluding patients given glycaemic rescue therapy.

¶ Not statistically significant (p≥0.05) compared to placebo + metformin.

In combination with metformin, sitagliptin provided significant improvements in HbA_{1c} (the primary endpoint), FPG, and 2-hour PPG compared to placebo with metformin (Table 2). A pre-specified secondary endpoint was the number of patients in each group who required therapeutic "rescue" with pioglitazone. Twenty-one of 464 patients (5%) randomised to sitagliptin and 32 of 237 patients (14%) randomised to placebo required pioglitazone "rescue". The improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c}, prior antihyperglycaemic therapy, gender, age, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Compared to patients taking placebo, patients taking sitagliptin demonstrated slight decreases in total cholesterol, non-HDL choelsterol and TG. A similar decrease in body weight was observed for both treatment groups.

Active-Controlled Study Against Glipizide as Add-on Therapy to Metformin

Long-term maintenance of effect was evaluated in a 52-week, double-blind, glipizide-controlled trial in patients with type 2 diabetes. Patients with inadequate glycaemic control on metformin at ≥1,500 mg/day were randomised to treatment with sitagliptin 100 mg daily (N=588) or glipizide (N=584) 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 optimise glycaemic control. Thereafter, the glipizide dose was to have been kept constant. The mean dose of glipizide after the titration period was 10.3 mg.

The objective of the study was to test whether sitagliptin was not inferior to glipizide, at a non-inferiority margin of 0.3%. After 52 weeks, both treatments resulted in a statistically significant improvement in glycaemic control from baseline. The reduction from baseline in HbA_{1c} (primary endpoint) was -0.67% for sitagliptin 100 mg daily and -0.67% for glipizide, confirming the non-inferiority of sitagliptin compared to glipizide. With respect to other analyses, the reduction in FPG was -0.56 mmol/L for sitagliptin and -0.42 mmol/L for glipizide. In a post-hoc analysis, patients with higher baseline HbA_{1c} (≥9%) in both groups had greater reductions from baseline in HbA_{1c} (sitagliptin, -1.68%; glipizide, -1.76%). The incidence of hypoglycaemia in the sitagliptin group (4.9%) was significantly 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 Therapy to Pioglitazone

A total of 353 patients with type 2 diabetes inadequately controlled on pioglitazone alone participated in a 24-week, randomised, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with pioglitazone. All patients were started on pioglitazone monotherapy at a dose of 30-45 mg per day. Patients were randomised to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Glycaemic endpoints measured included HbA_{1c} and fasting glucose. Another pre-specified secondary endpoint was the number of patients in each group who required therapeutic "rescue" with metformin.

In combination with pioglitazone, sitagliptin provided significant improvements in HbA_{1c} and FPG compared to placebo with pioglitazone (Table 3). The improvement in HbA_{1c} compared to placebo was not affected by baseline HbA_{1c}, prior antihyperglycaemic therapy, gender, age, race, baseline BMI, length of time since diagnosis of diabetes, presence of metabolic syndrome, or standard indices of insulin resistance (HOMA-IR) or insulin secretion (HOMA-β). Compared to patients taking placebo, patients taking sitagliptin demonstrated a slight decrease in TG. There was no significant difference between sitagliptin and placebo in body weight change. Twelve of 175 patients (7%) randomised to sitagliptin and 25 of 178 patients (14%) randomised to placebo required metformin "rescue".

Table 3 Glycaemic Parameters and Body Weight at Final Visit (24-Week Study) for Sitagliptin in Combination with Pioglitazone† - Primary (HbA_{1C}) and Secondary Outcomes

	Sitagliptin 100 mg + Pioglitazone	**Placebo + Pioglitazone**
HbA_{1c} (%)	**N = 163**	**N = 174**
Baseline (mean)	8.05	8.00
Change from baseline (adjusted mean‡)	-0.85	-0.15
Difference from placebo + pioglitazone	-0.70§	
Patients (%) achieving HbA_{1c} <7%	74 (45.4)	40 (23.0)
FPG (mmol/L)	**N = 163**	**N = 174**
Baseline (mean)	9.34	9.19
Change from baseline (adjusted mean‡)	-0.93	0.06
Difference from placebo + pioglitazone	-0.98§	
Body Weight (kg)%	**N = 133**	**N = 136**
Baseline (mean)	90.0	85.6
Change from baseline (adjusted mean‡)	1.8	1.5
Difference from placebo + pioglitazone	0.2¶	

† All Patients Treated Population (an intention-to-treat analysis).

‡ Least squares means adjusted for prior antihyperglycaemic therapy status and baseline value.
§ p<0.001 compared to placebo + pioglitazone.
% All Patients as Treated (APaT) population, excluding data following glycaemic rescue therapy.
¶ Not statistically significant (p≥0.05) compared to placebo + pioglitazone.

Simvastatin

Coronary Heart Disease (CHD)

In two large, placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study (4S, N=4,444 patients) and the Heart Protection Study (HPS, N=20,536 patients), the effects of treatment with simvastatin were assessed in patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Simvastatin was proven to reduce: the risk of total mortality by reducing CHD deaths; the risk of non-fatal myocardial infarction (MI) and stroke; and the need for coronary and non-coronary revascularisation procedures.

In 4S, the effect of therapy with simvastatin on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 5.5-8.0 mmol/L. In this multicenter, randomised, double-blind, placebo-controlled study, patients with angina or a previous MI were treated with diet, standard care, and either simvastatin 20-40 mg/day (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. Eighty-two percent (82%) of the subjects were male. 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 reduced the risk of death by 30%, 95% confidence interval (CI) 15-42%, p=0.0003 (182 deaths in the simvastatin group vs 256 deaths in the placebo group). The risk of CHD death was reduced by 42%, 95% CI 27-54%, p=0.00001 (111 vs 189 deaths). Simvastatin also decreased the risk of having major coronary events (CHD death plus hospital-verified and silent non-fatal MI) by 34%, 95% CI 25-41%, 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 reduced the risk for undergoing myocardial revascularisation procedures (coronary artery bypass grafting [CABG] or percutaneous transluminal coronary angioplasty [PTCA]) by 37%, 95% CI 26-46%, p<0.00001 (252 vs 383 patients). Furthermore, simvastatin significantly reduced the risk of fatal plus non-fatal cerebrovascular events (stroke and transient ischemic attacks [TIAs]) by 28%, 95% CI 3-46%, p=0.033 (75 vs 102 patients). There was no statistically significant difference between groups in non-cardiovascular mortality. Simvastatin reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL-C levels. The risk of death in patients ≥60 years of age was decreased by 27%, and in patients <60 years of age by 37%, 95% CI 12-55% (p<0.01 in both age groups). Because there were only 53 female deaths, the effect of simvastatin on mortality in women could not be adequately assessed. However, simvastatin lessened the risk of having major coronary events by 34%, 95% CI 9-52%, p=0.012 (60 vs 91 women with one or more event). In a post-hoc analysis in patients with diabetes mellitus and CHD, the risk of major coronary events was reduced by 55%, 95% CI 24-73%, p=0.002 (24 patients vs 44 patients). Since there were only 39 deaths among diabetic patients (15 among simvastatin-treated patients and 24 among placebo treated patients), the effect of simvastatin on mortality in diabetic patients could not be adequately assessed. It should be noted that 4S excluded patients with triglycerides >2.5 mmol/L or with severe cardiac or renal disease.

In the Multicenter Anti-Atheroma Study (MAAS)**,** the effect of therapy with simvastatin on coronary atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolaemic men and women with coronary heart disease. In this randomised,

double-blind, controlled clinical trial, 404 patients with total-C values of 5.5 to 8.0 mmol/L and a mean baseline LDL-C value of 4.4 mmol/L were treated with conventional measures and with simvastatin 20 mg/d or placebo. Eighty-nine percent (89%) of the subjects were male. Angiograms were evaluated at baseline, two and four years. A total of 347 patients had a baseline angiogram and at least one follow-up angiogram. In the patients who received placebo, coronary atherosclerotic lesions worsened in a near-linear manner. In contrast, simvastatin significantly slowed the progression of lesions as measured in the final angiogram by the mean change per-patient in minimum (p=0.005) and mean (p=0.026) lumen diameters (co-primary endpoints, indicating focal and diffuse disease, respectively), as well as in percent diameter stenosis (p=0.003). Simvastatin also significantly decreased the proportion of patients with new lesions (13% simvastatin vs 24% placebo, p=0.009) and with new total occlusions (5% vs 11%, p=0.04). In interpreting these results, it is important to be aware of the limitations of angiography, which may underestimate the extent and severity of atherosclerosis. In addition, angiography cannot be used to predict the site of future coronary occlusion. Acute ischaemic events tend to occur not at the site of severe stenoses but at lesser stenoses which are lipid-rich, soft and more prone to rupture. In MAAS, simvastatin slowed the progression of coronary atherosclerosis and reduced the development of both new lesions and new total occlusions, whereas coronary atherosclerotic lesions steadily worsened over four years in patients receiving standard care.

High Risk of CHD or Existing CHD

HPS was a large, multicenter, randomised, placebo-controlled, double-blind study with a mean duration of 5.3 years conducted in 20,536 patients (10,269 on simvastatin 40 mg and 10,267 on placebo), including 5,963 patients with diabetes mellitus (2,978 on simvastatin and 2,985 on placebo). Patients were 40-80 years of age and at high risk of developing a major coronary event based on 3 main categories of past medical history: *coronary disease* (definite or probable clinical diagnosis of MI, unstable angina, stable angina, PTCA or CABG); *occlusive disease of non-coronary arteries* (clinical, angiographic or ultrasound diagnosis of carotid artery stenosis (e.g. TIA or non-disabling stroke not thought to be haemorrhagic), carotid endarterectomy, leg artery stenosis (e.g. intermittent claudication) or surgery); or *diabetes mellitus* (clinical diagnosis of insulin-dependent or maturity-onset diabetes). LDL-C levels were assayed using a direct method and collected without regard for meals (results are about 5% lower than fasting sample). At baseline, 3,421 patients (17%) had LDL-C levels below 2.6 mmol/L; 7,068 patients (34%) had levels greater than 2.6 mmol/L and less than 3.4 mmol/L; and 10,047 patients (49%) had levels greater than or equal to 3.4 mmol/L. At baseline, 2,030 (19.8%) patients in the simvastatin group and 2,042 (19.9%) in the placebo group had total-C less than 5.0 mmol/L; 3,942 (38.4%) patients in the simvastatin group and 3,941 (38.4%) in the placebo group had levels greater than or equal to 5.0 mmol/L and less than 6.0 mmol/L; and 4,297 (41.8%) patients in the simvastatin group and 4,284 (41.7%) in the placebo group had levels greater than or equal to 6.0 mmol/L.

Table 4 Summary of Risk Reductions in HPS

Endpoint	Simvastatin (N=10,269)	Placebo (N=10,267)	Absolute Risk Reduction† % (95% CI)	Relative Risk Reduction % (95% CI)	P value
Primary					
Mortality	1,328 (12.9%)	1,504 (14.6%)	1.7 (0.8 to 2.7)	12 (6-19)	p<0.001
CHD mortality	571 (5.6%)	689 (6.7%)	1.2 (0.5 to 1.8)	18 (8-26)	p<0.001
Non-CHD mortality	757 (7.4%)	815 (7.9%)	0.6 (-0.2 to 1.3)	8 (-2 to 17)	NS
Secondary					
Major vascular events‡, §	2,026 (19.7%)	2,575 (25.1%)	5.4 (4.2 to 6.5)	24 (19-28)	p<0.00001
Major coronary events‡, %	892 (8.7%)	1,205 (11.7%)	3.1 (2.2 to 3.9)	27 (21-33)	p<0.00001
Stroke	448 (4.4%)	588 (5.7%)	1.4 (0.8 to 2.0)	25 (15-33)	p<0.00001
Key Tertiary					
Coronary revascularisation	511 (5.0%)	729 (7.1%)	2.1 (1.5 to 2.8)	31 (23-38)	p<0.00001
Hospitalisation for angina	1,036 (10.1%)	1,221 (11.9%)	1.8 (0.9 to 2.7)	17 (9-23)	p<0.0001

† Based on difference in crude event rates

‡ See Figure 2 (results by baseline characteristics)

§ A composite of non-fatal myocardial infarction, CHD death, stroke, or revascularisation procedures

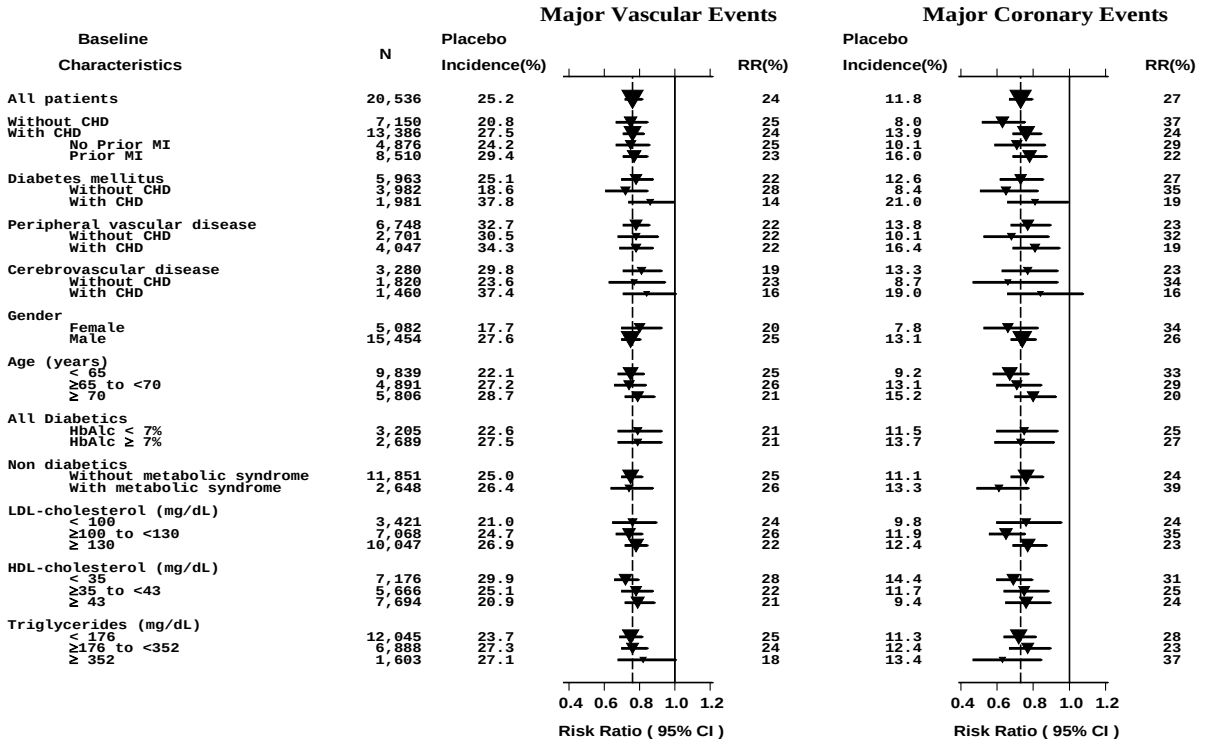
% A composite of non-fatal myocardial infarction or CHD deaths

NS = not statistically significant

The major cardiovascular events prevented were non-fatal myocardial infarction, CHD death, stroke and revascularisation procedures. The HPS results showed that simvastatin 40 mg/day significantly reduced: total and CHD mortality (with no evidence of any increase in non-CHD mortality); major coronary events (a composite endpoint comprised of non-fatal MI or CHD deaths); stroke; coronary revascularisation procedures; hospitalisation for angina; and major vascular events, a composite endpoint which was comprised of major coronary events, stroke, or revascularisation procedures (see Table 4). Risk reductions of approximately one-quarter were observed for major vascular events, major coronary events, and stroke. These risk reductions are underestimates due to the fact that 33% of the patients in the intention-to-treat analysis did not comply with the study protocol (i.e., patients allocated placebo took a statin, or patients allocated simvastatin did not take the study medication). Thus, by five years, simvastatin taken consistently would be expected to reduce the risk of these events by at least one-third.

Simvastatin also reduced the risk of peripheral macrovascular complications of diabetes, a composite endpoint comprised of peripheral revascularisation procedures, lower limb amputations or leg ulcers, by 21% (95% CI 2-36%, p=0.0293). The effects of simvastatin on major vascular events and major coronary events were similar in all subgroups of patients (see Figure 2). Among the diabetic participants, results for other endpoints measured were generally consistent with other high-risk individuals studied in HPS, including relative risk reductions of 20% for coronary mortality, 37% for non-fatal MI, 24% for stroke, and 17% for revascularisations ($p \leq 0.02$). The risk reductions produced by simvastatin in both major coronary events and major vascular events were evident and consistent across all baseline characteristics shown in Figure 2. In addition, these risk reductions were evident and consistent regardless of prior treated hypertension, creatinine levels up to the entry limit of 203 mmol/L, apolipoprotein A-I and B levels, baseline concomitant cardiovascular medications (i.e., ASA, beta blockers, ACE inhibitors, or calcium channel blockers), smoking status, alcohol intake, or obesity.

Figure 2 The Beneficial Effects of Treatment with Simvastatin on Major Vascular Events and Major Coronary Events in HPS



N= number of patients in each subgroup. All subgroups were defined at baseline. In this study, patients were classified with metabolic syndrome if they had abdominal obesity, elevated blood pressure, and low HDL-C; other factors such as fasting TG and insulin resistance were not measured. Placebo incidence is the percentage of patients in the placebo group who had one or more MVE or MCE during the study. The inverted triangles are point estimates of the risk ratio in the simvastatin group, with their 95% confidence intervals represented as a line. If the point estimate fell on the left of the unity line, the observed outcome was better in patients allocated active simvastatin. Conversely, if it fell on the right, the observed outcome was better in patients allocated placebo. The areas of the triangles are proportional to the number of patients with the relative endpoint. The vertical dashed line represents the point estimate of relative risk in the entire study population. RR(%) represents risk reduction, i.e., (1–risk ratio) x 100%.

Primary Hypercholesterolaemia and Combined Hyperlipidaemia (Fredrickson type IIa and IIb)

Simvastatin has been studied in the treatment of primary hypercholesterolaemia where diet alone has been insufficient. Simvastatin was highly effective in reducing total-C and LDL-C in heterozygous familial (Fredrickson type IIa) and non-familial forms of hypercholesterolaemia, and in mixed hyperlipidaemia (Fredrickson type IIb) when elevated cholesterol was a cause of concern. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response has been maintained during continuation of therapy. In six controlled clinical studies involving approximately 1,700 patients with normal or slightly raised TG (mean 1.9 mmol/L), plasma TG, VLDL-C and Apo B decreased in all studies in a dose-dependent manner. In two of these studies in patients with hypercholesterolaemia receiving simvastatin 20 or 40 mg/day for 12 weeks, the following results were observed.

Table 5 Effect of Simvastatin in Patients with Hypercholesterolaemia

	Mean Baseline	Mean Percent Change	
		20 mg once daily (n=166)	40 mg once daily (n=161)
Total Cholesterol	8.3 mmol/L	-27: -27	-30: -33
LDL-Cholesterol	6.4 mmol/L	-32: -34	-40: -41
HDL-Cholesterol	1.2 mmol/L	+10: +10	+10: +13
Triglycerides	1.9 mmol/L	-13: -17	-19: -27
VLDL-Cholesterol	0.8 mmol/L	-8[1]*	-28[2]*
Apolipoprotein B	2000 mg/L	-28: -33	-36: -38

[1] (n=84)
[2] (n=81)
* only measured in one study

In a separate study involving 180 patients with combined hyperlipidaemia, simvastatin 10 mg/day for 17 weeks was also shown to be effective in lowering total-C, LDL-C, VLDL-C, TGs and Apo B.

Table 6 Effect of Simvastatin in Patients with Combined Hyperlipidaemia

	Mean Baseline	Mean Percent Change
		10 mg once daily (n=56)
Total Cholesterol	7.0 mmol/L	-23
LDL-Cholesterol	4.5 mmol/L	-27
HDL-Cholesterol	1.0 mmol/L	+13
Triglycerides[1]	2.6 mmol/L	-26
VLDL-Cholesterol	1.3 mmol/L	-28
Apolipoprotein B	1710 mg/L	-21

[1] median

The data from these studies demonstrate that in patients with hypercholesterolaemia and normal or slightly raised TG, simvastatin consistently reduces total-C, LDL-C, TG, VLDL-C and Apo B in a dose dependent manner. The results of 4 separate studies depicting the dose response to simvastatin in patients with primary hypercholesterolaemia are presented in Table 7.

In the Upper Dose Comparative Study, the percent reduction in LDL-C was essentially independent of the baseline level. In contrast, the percent reduction in TG was related to the baseline level of TG. In this study, patients with TG > 4.0 mmol/L were excluded.

The value of medication- and/or diet-induced reduction in plasma cholesterol is no longer controversial. The benefits of reducing LDL-C on morbidity and mortality due to CHD have been established. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) demonstrated in a seven-year, double-blind, placebo-controlled study that lowering LDL-C with diet and cholestyramine decreased the combined incidence of CHD death plus non-fatal MI.

Table 7 Dose Response in Patients with Primary Hypercholesterolaemia - Mean Percent Change from Baseline After 6 to 24 Weeks

	N	Total-C	LDL-C	HDL-C	TG*
Lower Dose Comparative Study					
Simvastatin 5 mg**	109	-19	-26	10	-12
Simvastatin 10 mg**	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study					
Placebo	2,223	-1	-1	0	-2
Simvastatin 20 mg**	2,221	-28	-38	8	-19
Upper Dose Comparative Study					
Simvastatin 40 mg**	433	-31	-41	9	-18
Multicenter Combined Hyperlipidaemia Study					
Placebo	122 (except LDL-C, N=121)	1	2	3	-4
Simvastatin 40 mg**	122	-25	-29	13	-28

* median percent change

** in the evening

Hypertriglyceridaemia (Fredrickson type IV hyperlipidaemia)

The results of subgroup analyses from a study including a total of 116 patients with hypertriglyeridaemia (Fredrickson type IV hyperlipidaemia) are presented in Table 8. This study was a double-blind and placebo-controlled parallel study. Each treatment group included approximately 30 patients. The respective baseline values for the type IV patients were: total-C = 6.04 mmol/L; LDL-C = 2.59 mmol/L; HDL-C = 0.91 mmol/L; TG = 5.01 mmol/L; VLDL-C = 2.44 mmol/L; non-HDL-C = 5.13 mmol/L.

Table 8 Six-week, Lipid-lowering effects of Simvastatin in Type IV Hyperlipidaemia - Mean Percent Change from Baseline**

	Total-C	LDL-C	HDL-C	TG*	VLDL-C*	Non-HDL-C
Placebo	0	3	3	-13	-10	-1
Simvastatin 20 mg/day	-21	-23	9	-21	-33	-26
Simvastatin 40 mg/day	-26	-25	9	-21	-35	-32

* median percent change

** approximately 30 patients in each treatment group

Dysbetalipoproteinaemia (Fredrickson type III hyperlipidaemia)

Table 9 presents the subgroup analysis results of 7 patients with Fredrickson type III hyperlipidaemia (dysbetalipoproteinaemia; apo E2/2 and VLDL-C/TG >0.25) from a 130-patient double-blind, placebo-controlled crossover study. In this study the median baseline values were: total-C = 8.39 mmol/L, LDL-C (+IDL) = 3.13 mmol/L, HDL-C = 0.80 mmol/L, TG = 4.67 mmol/L, VLDL-C (+IDL) = 4.40 mmol/L, and non-HDL-C = 7.54 mmol/L.

Table 9 Six-week, Lipid-lowering Effects of Simvastatin in Type lll Hyperlipidaemia - Median Percent Change from Baseline

	Total-C	LDL-C*	HDL-C	TG	VLDL-C*	Non-HDL-C
Placebo	-8	-8*	-2	+4	-4*	-8
Simvastatin 40 mg/day	-50	-50*	+7	-41	-58*	-57

* includes IDL

Homozygous Familial Hypercholesterolaemia

In a controlled clinical study, 4 patients, 19-27 years of age, with homozygous familial hypercholesterolaemia 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%.

INDICATIONS

JUVICOR (sitagliptin and simvastatin) is indicated in adult patients with type 2 diabetes mellitus in whom treatment with both sitagliptin and simvastatin is indicated according to the separate indications of these drugs.

The indications for sitagliptin are:

- For the treatment of type 2 diabetes mellitus in persons 18 years of age and older who have failed dietary measures and exercise as dual combination therapy with metformin, or with a sulfonylurea, or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

The indications for simvastatin are:

- Simvastatin is indicated as an adjunct to diet for treatment of hypercholesterolaemia.

  Prior to initiating therapy with simvastatin, secondary causes of hypercholesterolaemia (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinaemias, obstructive liver disease, other drug therapy, alcoholism) should be identified and treated.
- Simvastatin is indicated in patients at high risk of CHD (with or without hypercholesterolaemia) including patients with history of stroke or other cerebrovascular disease, peripheral vessel disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke, and hospitalisation due to angina pectoris.

  These effects do not replace the need to independently control known causes of cardiovascular mortality and morbidity such as hypertension, diabetes and smoking.

CONTRAINDICATIONS

- Hypersensitivity to any component of this preparation (see **PRECAUTIONS**, *Hypersensitivity Reactions*; **ADVERSE EFFECTS**, *Post-marketing Experience*).
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and lactation (see **PRECAUTIONS**, *Use in Pregnancy, Use in Lactation*).
- Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) (see **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*; **INTERACTIONS WITH OTHER MEDICINES**, *Simvastatin*).
- Concomitant administration of gemfibrozil, cyclosporin, or danazol (see **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*; **INTERACTIONS WITH OTHER MEDICINES**, *Simvastatin)*.
- Myopathy secondary to other lipid lowering agents.

- Concomitant use with fusidic acid (see **PRECAUTIONS**; **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS
JUVICOR should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Myopathy/Rhabdomyolysis
Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X 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 HMG-CoA reductase inhibitory activity in plasma. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

In 4S, there was one case of myopathy among 1,399 patients taking simvastatin 20 mg/day and no cases among 822 patients taking 40 mg/day for a median duration of 5.4 years. In two 6 month controlled clinical studies, there was one case of myopathy among 436 patients taking 40 mg and 5 cases among 669 patients taking 80 mg.

As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related for simvastatin. 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%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a major, large, long-term clinical trial (SEARCH) in which patients with a history of MI were treated with simvastatin 80 mg/day (mean follow-up 6.7 years), the incidence of myopathy was approximately 1.0% compared with 0.02% for patients on 20 mg/day. This includes rhabdomyolysis for which the incidence was 0.1 to 0.2%, all allocated to simvastatin 80 mg/day. There is no universally accepted definition of rhabdomyolysis. In SEARCH, rhabdomyolysis was defined as a subset of myopathy with CK > 40x ULN plus evidence of end organ damage (e.g. elevated creatinine, dark urine). Approximately half of all the myopathy cases occurred during the first year of treatment. The incidence of myopathy during each subsequent year of treatment was approximately 0.1%.

All patients starting therapy with simvastatin, or whose dose of JUVICOR is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. JUVICOR therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms and a CK level > 10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with JUVICOR or whose dose 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 insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with

JUVICOR should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

The risk of myopathy/rhabdomyolysis is increased by concomitant use of simvastatin with the following medicines:

Contraindicated medicines

- **Potent inhibitors of CYP3A4:** Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 at therapeutic doses (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir, or nefazodone) is contraindicated. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Potent inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy. If short-term treatment with potent CYP3A4 inhibitors is unavoidable, therapy with JUVICOR should be suspended during the course of treatment. If JUVICOR is suspended during treatment with any of these agents, consideration should be given to the use of sitagliptin (JANUVIA®) to maintain glycaemic control until JUVICOR can be reinstated (see **CONTRAINDICATIONS**; **INTERACTIONS WITH OTHER MEDICINES**, *Simvastatin*).
- **Gemfibrozil, cyclosporin or danazol:** Concomitant use of these medicines with JUVICOR is contraindicated (see **CONTRAINDICATIONS**).
- **Fusidic acid:** Patients on fusidic acid treated concomitantly with JUVICOR may have an increased risk of myopathy/rhabdomyolysis (see **INTERACTIONS WITH OTHER MEDICINES**). Fusidic acid must not be co-administered with statins (see **CONTRAINDICATIONS**). In patients where the use of systemic fusidic acid is considered essential, JUVICOR should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. JUVICOR therapy may be reintroduced seven days after the last dose of fusidic acid. Consideration should be given to the use of sitagliptin (JANUVIA) to maintain glycaemic control until JUVICOR can be reinstated.

Other medicines

- **Amiodarone:** In a clinical trial, myopathy was reported in 6% of patients receiving simvastatin 80 mg and amiodarone. In the same clinical trial, there were no cases of myopathy reported in patients receiving simvastatin 20 mg and amiodarone. **The dose of JUVICOR should not exceed 100/20 mg daily in patients receiving concomitant medication with amiodarone** (see Table 10; **DOSAGE AND ADMINISTRATION**; **INTERACTIONS WITH OTHER MEDICINES**, *Simvastatin*)
- **Calcium channel blockers:**

  Verapamil or diltiazem: The dose of JUVICOR should not exceed 100/20 mg daily in patients receiving concomitant medication with verapamil or diltiazem (see Table 10; **DOSAGE AND ADMINISTRATION**; **INTERACTIONS WITH OTHER MEDICINES**, *Simvastatin*).

  Amlodipine: In a clinical trial, patients on amlodipine treated concomitantly with simvastatin 80 mg had a slightly increased risk of myopathy. The risk of myopathy in patients taking simvastatin 40 mg was not increased by concomitant amlodipine (see **INTERACTIONS WITH OTHER MEDICINES**, *Simvastatin*).
- **Moderate inhibitors of CYP3A4:** Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with JUVICOR, particularly at

higher doses of the simvastatin component, may have an increased risk of myopathy. When co-administering JUVICOR with a moderate inhibitor of CYP3A4, a dose adjustment of JUVICOR may be necessary.

- **Other fibrates: The dose of JUVICOR should not exceed 100/10 mg daily in patients receiving concomitant medication with other fibrates (except fenofibrate.)** When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. Caution should be used when prescribing fenofibrate with JUVICOR, as either agent can cause myopathy when given alone. Addition of fibrates to simvastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates with simvastatin have been used without myopathy in small short-term clinical studies with careful monitoring.
- **Niacin (≥1 g/day):** Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin. In an on-going, double-blind, randomised cardiovascular outcomes trial conducted in China, the United Kingdom and Scandinavia, an interim analysis by the independent safety monitoring committee revealed that the incidence of myopathy among approximately 4,700 UK/Scandinavian patients treated with either simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg coadministered with extended-release (ER) niacin/laropiprant 2 g/40 mg is similar to the overall incidence reported in the clinical trial database for simvastatin 40 mg (0.08%). However, in approximately 3,900 Chinese patients in the same treatment arm, the incidence appears to be substantially higher than expected. The risk of myopathy was not increased among 8600 Chinese, UK, or Scandinavian patients in the control arm (placebo and simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg). Because the incidence of myopathy is higher in Chinese than in non-Chinese patients, caution should be used when treating Chinese patients with JUVICOR (particularly at the dose of 100/40 mg) co-administered with lipid-modifying doses (≥1 g/day) of niacin or niacin-containing products. It is unknown whether there is an increased risk of myopathy with coadministration in other Asian patients.

Prescribing recommendations for interacting agents are summarised in Table 10 (further details are provided in the text (see also **INTERACTIONS WITH OTHER MEDICINES**; **PHARMACOLOGY**).

Table 10 Interactions with Other Medicines that are Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Potent CYP3A4 inhibitors, e.g.: Itraconazole Ketoconazole Posaconazole Voriconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Boceprevir Telaprevir Nefazodone Cyclosporin Danazol Gemfibrozil Fusidic acid	Contraindicated with JUVICOR
Other fibrates (except fenofibrate)	Do not exceed 100/10 mg JUVICOR daily
Amiodarone Verapamil Diltiazem	Do not exceed 100/20 mg JUVICOR daily
Grapefruit juice	Avoid grapefruit juice

Pancreatitis
In post-marketing experience there have been reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotising pancreatitis (see **ADVERSE EFFECTS**, *Post-marketing Experience*), in patients taking sitagliptin. Because these reports are made voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin. If pancreatitis is suspected, JUVICOR and other potentially suspect medicinal products should be discontinued.

Use in Patients with Renal Insufficiency
Sitagliptin is renally excreted. As appropriate dose strengths of JUVICOR are not available, use of JUVICOR in patients with moderate or severe renal insufficiency (CrCl <50 mL/min) or ESRD should be avoided (see **DOSAGE AND ADMINISTRATION**, *Patients with Renal Insufficiency*).

Hypoglycaemia in Combination with a Sulfonylurea
In clinical trials of sitagliptin as monotherapy and as part of combination therapy with agents not known to cause hypoglycaemia (i.e. metformin or a PPARγ agonist [thiazolidinedione], rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. As is typical with other antihyperglycaemic agents, when sitagliptin was used in combination with a sulfonylurea, a medication known to cause hypoglycaemia, the incidence of sulfonylurea-induced hypoglycaemia was increased over that of placebo (see **ADVERSE EFFECTS**). Therefore, to reduce the risk of sulfonylurea- induced hypoglycaemia, a lower dose of sulfonylurea may be considered (see **DOSAGE AND ADMINISTRATION**).

Hepatic Effects
In clinical studies, persistent increases (to more than 3X ULN) in serum transaminases have occurred in 1% of adult patients who received simvastatin. When the medication was interrupted or discontinued in these patients, transaminases usually fell slowly to pre-treatment concentration. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. Some of these patients had abnormal liver function tests (LFTs) prior to therapy with simvastatin and/or consumed substantial quantities of alcohol.

In 4S (see **CLINICAL TRIALS**, *Simvastatin*), the number of patients with more than one ALT 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%]). The incidence of ALT elevations in simvastatin subjects was greater than the incidence of AST elevations and the number of subjects with at least one elevation of ALT greater than 3 X ULN was 46 (2.2%) in the simvastatin group and 32 (1.4%) in the placebo group, the difference not being statistically significant. The frequency of single elevations of ALT to 3X ULN was significantly higher in the simvastatin group in the first year of the study (20 vs 8, p=0.023), but not thereafter. Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin patients in 4S with normal LFTs at baseline, only 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. 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 6-month incidence of persistent hepatic transaminase elevations considered medication related was 0.7% and 1.8% at the 40 mg and 80 mg dose, respectively.

In HPS (see **CLINICAL TRIALS**, *Simvastatin*), in which 20,536 patients were randomised to receive simvastatin 40 mg/day or placebo, the incidences of elevated transaminases (>3X ULN confirmed by repeat test) were 0.21% (n=21) for patients treated with simvastatin and 0.09% (n=9) for patients treated with placebo.

LFTs should be performed before the initiation of treatment and thereafter when clinically indicated. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy (see **PRECAUTIONS***, Myopathy/ Rhabdomyolysis).*

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 hyperbilirubinaemia or jaundice occurs during treatment with JUVICOR, promptly interrupt therapy. If an alternate aetiology is not found, do not restart JUVICOR.

Patients who develop increased transaminase levels should have the finding confirmed and be followed thereafter with frequent liver tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3X ULN persist, withdrawal of JUVICOR therapy is recommended. Liver biopsy should be considered if elevations persist despite discontinuation of the medicine. Unconfirmed reports of "medicine-induced hepatitis" have been reported with simvastatin.

JUVICOR 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 JUVICOR.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes were not specific to simvastatin and were observed with comparative lipid-lowering agents. They generally appeared within 3 months after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Interstitial Lung Disease
Cases of interstitial lung disease have been reported with some statins, including simvastatin especially with long term therapy (see **ADVERSE EFFECTS**). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, therapy with JUVICOR should be discontinued because JUVICOR contains simvastatin. Consideration should be given to the use of sitagliptin (JANUVIA) to maintain glycaemic control if JUVICOR is discontinued.

Hypersensitivity Reactions
There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. 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 exposure to sitagliptin. 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 JUVICOR, assess for other potential causes for the event, and institute alternative treatment (see **CONTRAINDICATIONS**; **ADVERSE EFFECTS**, *Post-marketing Experience*).

Ophthalmic Evaluations
Current long-term data from clinical studies, e.g. 4S, do not indicate an adverse effect of simvastatin on human lens. However, the very long-term effects are not yet established and therefore periodic ophthalmic examinations are recommended after five years of treatment, taking into consideration that in the absence of any pharmacotherapy, an increase in the prevalence of lens opacities with time is expected as a result of aging.

Animal studies
Cataracts have been detected in 2 year studies in rats and dogs at dose levels greater than 25 and 10 mg/kg/day, respectively, although at a very low incidence. While there is no clear correlation between the magnitude of serum lipid-lowering and the development of cataracts, a consistent relationship has been observed between high serum levels and cataract development with simvastatin and related HMG-CoA reductase inhibitors.

Serum levels (expressed as total inhibitors) in rats at the no-effect dose level were 3-11 times higher than those in humans receiving a simvastatin dose of 80 mg, whereas serum levels at the no-effect level in dogs were approximately two-fold higher than those in humans receiving a dose of 80 mg.

Thyroid Function
The concentration of serum thyroxine has been measured at baseline and at the end of simvastatin treatment in 785 patients enrolled in multicentre studies. The results of this analysis indicate that simvastatin has little if any effect upon thyroxine activity.

In one study involving 183 patients treated with simvastatin, four patients had TSH levels within the normal range before commencing simvastatin, but had an elevated TSH after two years of simvastatin therapy.

Transient Hypotension
Three cases of symptomatic hypotension in the first few days following the start of simvastatin therapy have been reported. Two of the patients were on antihypertensive medication. The hypotension resolved with continued therapy with simvastatin.

Neurological Effects
The neurological adverse effects reported to date include cases of peripheral neuropathy and paraesthesia possibly due to simvastatin.

Effects on Fertility
No adverse effects on fertility were observed in male and female rats given ***sitagliptin*** orally at doses up to 1000 mg/kg daily (approximately 100 times the AUC in humans at the clinical dose of 100 mg/day) prior to and throughout mating.

In several studies of over 800 men with hypercholesterolaemia treated with ***simvastatin*** 20 mg to 80 mg per day for 12 to 48 weeks, basal testosterone levels were mildly decreased during simvastatin therapy, but there were no consistent changes in LH and FSH. In 86 men treated with simvastatin 20 mg to 80 mg per day, there was no impairment of hCG-stimulated testosterone secretion. Testicular degeneration has been seen in two dog safety studies with simvastatin. Special studies designed to further define the nature of these changes have not met with success since the effects are poorly reproducible and unrelated to dose, serum cholesterol levels, or duration of treatment. Simvastatin has been administered for up to two years to dogs at a dose of 50 mg/kg/day without any testicular effects. Fertility of male and female rats was unaffected at oral doses up to 25 mg/kg/day.

Use in Pregnancy (Category D)
JUVICOR is contraindicated during pregnancy. There are no adequate and well-controlled studies of JUVICOR or its individual components in pregnant women; therefore, the safety of JUVICOR in pregnant women has not been established. Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering medicines during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolaemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG CoA reductase such as simvastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, JUVICOR should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant.

In two series of 178 and 134 cases where pregnant women took an HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy serious fetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and fetal deaths. The exact risk of injury to the fetus occurring after a pregnant woman is exposed to a HMG-CoA reductase inhibitor has not been determined. The current data do not indicate that the risk of fetal injury in women exposed to HMG-CoA reductase inhibitors is high. If a pregnant woman is exposed to a HMG-CoA reductase inhibitor, she should be informed of the possibility of fetal injury and discuss the implications with her pregnancy specialist (see **CONTRAINDICATIONS**).

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg/day or in rabbits given up to 125 mg/kg/day during organogenesis (up to 32 and 22 times, respectively, the AUC in humans at the clinical dose of 100 mg/day). A slight increase in the incidence of fetal rib abnormalities (absent, hypoplastic and wavy ribs) was observed among fetuses of rats given sitagliptin at 1000 mg/kg/day (approximately 100 times the AUC in humans at the clinical dose of 100 mg/day). Pups of rats administered sitagliptin at 1,000 mg/kg/day from gestation day 6 to lactation day 20 showed reduced birth weight and postnatal body weight gain (observed prior to and after weaning). No functional or behavioural toxicity was observed in the offspring of treated rats. Sitagliptin crosses the placenta in rats and rabbits.

Animal studies of ***simvastatin*** showed increased incidences of fetal resorption at doses of 50 mg/kg/day in rats and 15 mg/kg/day in rabbits. In another study, an increased incidence of skeletal malformations was observed in fetuses of rats dosed with the active metabolite of simvastatin, simvastatin acid, at a level of 60 mg/kg/day. The no-effect dose level of this teratogenic activity has not been established. Other inhibitors of HMG-CoA reductase have also been shown to induce skeletal malformations in rats, and the teratogenic effects may be due to the enzyme inhibitory activity of such medicines. The relevance of these findings to humans is not known.

Use in Lactation
Treatment of rats with ***sitagliptin*** during pregnancy and lactation caused decreased pup body weight gain (see **PRECAUTIONS**, *Use in Pregnancy*). Sitagliptin is excreted 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.

Animal studies have shown that weight gain during lactation is reduced in offspring of rats dosed with ***simvastatin*** at dosages of 12.5 to 25 mg/kg/day. There is no information from animal studies on whether simvastatin or its metabolites are excreted in breast milk.

Because many medicines are excreted in human milk and because of the potential for serious adverse reactions, women taking JUVICOR should not breast-feed their infants (see **CONTRAINDICATIONS**).

Paediatric Use
Safety and effectiveness of JUVICOR in paediatric patients under 18 years have not been established.

Use in the Elderly
In clinical studies, the safety and effectiveness of ***sitagliptin*** in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). Elderly patients are more likely to have renal insufficiency; as with other patients, dosage adjustment may be required in the presence of significant renal insufficiency (see; **DOSAGE AND ADMINISTRATION**, *Patients with Renal Insufficiency*).

In controlled clinical trials, the efficacy of ***simvastatin*** for patients over the age of 65 years, as assessed by reduction in total-C and LDL-C levels, was similar to that seen in the population as a whole. There was no apparent increase in the overall frequency of clinical or laboratory adverse findings. However, in a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥65 years of age had an increased risk of myopathy compared to patients <65 years of age.

Genotoxicity

Sitagliptin was not mutagenic or clastogenic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity assay, a chromosome aberration assay in Chinese hamster Ovary cells, an *in vitro* rat hepatocyte DNA alkaline elution assay (an assay which measures the compound's ability to induce single strand breaks in DNA), and an *in vivo* mouse micronucleus assay.

Genetic toxicology studies of ***simvastatin*** showed no evidence of mutagenic activity in bacteria or in mammalian cells *in vitro*, or of clastogenic activity *in vitro* or in mice *in vivo. In vitro* and *in vivo* assays showed that simvastatin does not cause DNA damage in rat hepatocytes.

Carcinogenicity

Sitagliptin

A two-year carcinogenicity study was conducted in rats given oral doses of sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of focal eosinophilic cellular alterations in the liver in both sexes at 150 mg/kg/day and at 500 mg/kg/day. There was an increased incidence of basophilic cellular alterations in females at 500 mg/kg/day. Eosinophilic and basophilic cellular alterations are regarded as preneoplastic lesions. There was an increase in hepatic adenomas and carcinomas in males, and hepatic carcinomas in females at 500 mg/kg/day. Systemic exposure in rats at 150 and 500 mg/kg/day are 19 and 58 times, respectively, that of humans at the 100 mg/day clinical dose. The no-observed effect level for induction of hepatic neoplasia was 150 mg/kg/day, producing exposure approximately 19-fold higher than the human exposure at the 100 mg/day clinical dose. The increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. The clinical significance of these findings for humans is unknown.

In a two-year carcinogenicity study conducted in mice, sitagliptin did not increase tumour incidence at oral doses up to 500 mg/kg/day (approximately 68 times the human exposure at the clinical dose of 100 mg/day).

Simvastatin

Carcinogenicity studies have been conducted in mice at oral doses ranging from 1 to 400 mg/kg/day and in rats at doses of 1 to 100 mg/kg/day. Hepatocellular adenomas and carcinomas were observed in both sexes of both species at doses greater than 25 mg/kg/day. Plasma simvastatin levels in rats at this no-effect dose level, expressed as the AUC for enzyme inhibitory activity, were 3 to 11 times greater than in humans at the maximum recommended dose of simvastatin whereas serum levels at the no-effect level in mice were similar to those in humans. Additional findings in mice were increased incidences of pulmonary adenomas at doses greater than 25 mg/kg/day, and of Harderian gland adenomas at 400 mg/kg/day. In rats, the incidence of thyroid follicular adenoma was increased in females at doses greater than 5 mg/kg/day and in males at doses greater than 25 mg/kg/day. These thyroid tumours were associated with focal cystic follicular hyperplasia, and may be a secondary effect reflective of a simvastatin-mediated enhancement of thyroid hormone clearance by the liver.

Effect on Laboratory Tests

The incidence of laboratory adverse experiences was similar in patients treated with ***sitagliptin*** 100 mg compared to patients treated with placebo. Across clinical studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC

vs placebo; mean baseline WBC approximately 6,600 cells/microL) was observed due to an increase in neutrophils. This observation was seen in most but not all studies. This change in laboratory parameters is not considered to be clinically relevant.

Marked and persistent increases of serum transaminases have been reported infrequently with use of ***simvastatin***. Elevated alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (GGT) have been reported. LFT abnormalities generally have been mild and transient. Increases in serum CK levels, derived from skeletal muscle, have been reported (see **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*). Increases in HbA_{1c} and fasting serum glucose levels have been reported with statins, including simvastatin.

INTERACTIONS WITH OTHER MEDICINES

Sitagliptin and simvastatin

The results of bioequivalence studies in healthy subjects demonstrated that JUVICOR (sitagliptin and simvastatin) is bioequivalent to co-administration of sitagliptin (JANUVIA®) and simvastatin (ZOCOR®) as individual tablets.

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

Digoxin

There was an increase in the AUC (26%) and C_{max} (41%) of digoxin with the co-administration of 100 mg sitagliptin and 80 mg simvastatin for 5 days. These increases are not considered to be clinically meaningful. No dosage adjustment of JUVICOR is recommended, but patients receiving digoxin should be monitored appropriately and the dosage adjusted if necessary.

Pharmacokinetic interaction studies involving JUVICOR and medications other than digoxin have not been performed; however, such studies have been conducted with the individual components of JUVICOR, sitagliptin and simvastatin.

Sitagliptin

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

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

- *Metformin:* Co-administration 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 glibenclamide, a CYP2C9 substrate, were 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 glibenclamide, are primarily eliminated by CYP2C9.
- *Thiazolidinediones:* Single-dose pharmacokinetics of rosiglitazone were not meaningfully altered in subjects receiving multiple daily doses of sitagliptin. Therefore, sitagliptin is not an inhibitor of CYP2C8-mediated metabolism. Clinically meaningful interactions with pioglitazone are not expected because pioglitazone predominantly undergoes CYP2C8- or CYP3A4-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. Since S(-) warfarin is primarily metabolised by CYP2C9, these data also support the conclusion that sitagliptin is not a CYP2C9 inhibitor.
- *Oral Contraceptives:* Co-administration with sitagliptin did not meaningfully alter the steady-state pharmacokinetics of norethindrone or ethinyl oestradiol.

Clinical data described below suggest that sitagliptin is not susceptible to clinically meaningful interactions by co-administered medications:

- *Metformin:* Co-administration of multiple twice-daily doses of metformin with sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.
- *Cyclosporin:* A study was conducted to assess the effect of cyclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of cyclosporin 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.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on the pharmacokinetics of sitagliptin. Medications assessed were those that are commonly administered to patients with type 2 diabetes including, but not restricted to, cholesterol-lowering agents (including statins, fibrates, ezetimibe), anti-platelet agents (including clopidogrel), antihypertensives (including ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (including naproxen, diclofenac, celecoxib), anti-depressants (including bupropion, fluoxetine, sertraline), antihistamines (including cetirizine), proton-pump inhibitors (including omeprazole, lansoprazole), and medications for erectile dysfunction (including sildenafil).

The safety and efficacy of sitagliptin in combination with insulin, GLP-1 mimetics, or alpha-glucosidase inhibitors has not been established. Sitagliptin has not been studied in combination with orlistat.

Simvastatin

CYP3A4 Interactions

Simvastatin is metabolised by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other medicines metabolised by CYP3A4.

Contraindicated medicines

Concomitant use of the following medicines is contraindicated:

Potent CYP3A4 inhibitors: Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of simvastatin. Concomitant use with medicines labelled as having a potent inhibitory effect on CYP3A4 (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, boceprevir, telaprevir or nefazodone) is contraindicated (see **CONTRAINDICATIONS**; **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*; **PHARMACOLOGY**, *Pharmacokinetics*).

Gemfibrozil, cyclosporin or danazol: (see **CONTRAINDICATIONS**; **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*).

Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of JUVICOR with fusidic acid. Co-administration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins. Where the use of fusidic acid is considered essential, JUVICOR should be discontinued throughout the duration of fusidic acid treatment (see **CONTRAINDICATIONS**; **PRECAUTIONS**; *Myopathy/Rhabdomyolysis*).

Other interactions

Amiodarone: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone with simvastatin (see **DOSAGE AND ADMINISTRATION**; **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*).

Calcium channel blockers: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil, diltiazem, or amlodipine (see **DOSAGE AND ADMINISTRATION**; **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*).

Moderate inhibitors of CYP3A4: Patients taking other medicines labelled as having a moderate inhibitory effect on CYP3A4 concomitantly with JUVICOR, particularly at higher doses of the simvastatin component, may have an increased risk of myopathy (see **PRECAUTIONS**; *Myopathy/Rhabdomyolysis*).

Niacin (nicotinic acid) (≥1 g/day): Cases of myopathy/rhabdomyolysis have been observed with simvastatin co-administered with lipid-modifying doses (≥1 g/day) of niacin (see **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*).

Colchicine*:* There have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal

insufficiency. Close clinical monitoring of patients taking colchicine and JUVICOR is advised.

Other Fibrates: The risk of myopathy is increased by gemfibrozil (see **CONTRAINDICATIONS**) and other fibrates (except fenofibrate); these lipid-lowering medicines can cause myopathy when given alone. When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent (see **CONTRAINDICATIONS**; **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*).

Grapefruit juice: Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of medicines metabolised by CYP3A4. The effect of typical consumption (one 250 ml glass daily) is minimal (13% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the AUC) and of no clinical relevance. However, because larger quantities significantly increase the plasma levels of HMG-CoA reductase inhibitory activity, grapefruit juice should be avoided during therapy with JUVICOR (see **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*).

Coumarin Derivatives: In two clinical studies, one in normal volunteers and the other in hypercholesterolaemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalised 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. In patients taking coumarin anticoagulants, prothrombin time should be determined before starting JUVICOR 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 JUVICOR is changed or JUVICOR 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.

Propranolol: In normal volunteers, concomitant administration of single doses of simvastatin with propranolol produced no clinically significant pharmacokinetic or pharmacodynamic interaction.

Antipyrine: Simvastatin had no effect on the pharmacokinetics of antipyrine. However, since simvastatin is metabolised by the CYP3A4, this does not preclude an interaction with other medicines metabolised by the same isoform.

Other concomitant therapy: In clinical studies, simvastatin was used concomitantly with beta-blockers, diuretics and non-steroidal anti-inflammatory medicines (NSAIDS) without evidence of clinically significant adverse interactions.

ADVERSE EFFECTS

In a pooled subgroup analysis of 19 controlled clinical studies of sitagliptin involving 1,582 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 or pioglitazone, the overall incidence of adverse reactions, hypoglycaemia, 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 hypoglycaemia (see Table 11); 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. Three 24-week, placebo-controlled add-on combination therapy studies, one with metformin, one with pioglitazone, and one with glimepiride with or without metformin, were also conducted. In addition to a stable dose of metformin, pioglitazone, glimepiride, or glimepiride and metformin, patients whose diabetes was not adequately controlled were given either sitagliptin 100 mg daily or placebo. The adverse reactions, reported regardless of investigator assessment of causality in ≥5% of patients treated with sitagliptin 100 mg daily as monotherapy, sitagliptin in combination with pioglitazone, or sitagliptin in combination with glimepiride, with or without metformin, and more commonly than in patients treated with placebo, are shown in Table 11.

Table 11 Placebo-Controlled Clinical Studies of Sitagliptin Monotherapy* or Add-on Combination Therapy with Pioglitazone or Glimepiride +/- Metformin: Adverse Reactions Reported in ≥5% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality†

Body System/Adverse Reactions	Number of Patients (%)	
	Sitagliptin 100 mg	**Placebo**
	N = 443	N = 363
Infections and Infestations		
Nasopharyngitis	23 (5.2)	12 (3.3)
	Sitagliptin 100 mg + Pioglitazone	**Placebo + Pioglitazone**
	N = 175	N = 178
Infections and Infestations		
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Nervous System Disorders		
Headache	9 (5.1)	7 (3.9)
	Sitagliptin 100 mg + Glimepiride (+/- Metformin)	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Metabolism and Nutrition disorders		
Hypoglycaemia	27 (12.2)	4 (1.8)
Infections and Infestations		
Nasopharyngitis	14 (6.3)	10 (4.6)
Nervous System Disorders		
Headache	13 (5.9)	5 (2.3)

† Intent to treat population

* Overall, the safety profile of the 200 mg daily dose was similar to that of the 100 mg daily dose.

In the 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 pre-specified 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 experiences of hypoglycaemia in patients treated with sitagliptin 100 mg was similar to placebo (1.2% vs 0.9%). Adverse experiences of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidence of selected gastrointestinal adverse reactions in patients treated with sitagliptin or placebo was as follows: abdominal pain (sitagliptin, 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), vomiting (0.8%, 0.9%), and diarrhoea (3.0%, 2.3%).

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

Pancreatitis

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomised to receive sitagliptin 100 mg/day (N=5,429) or corresponding (active or placebo) control (N=4,817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each

group (4 patients with an event in 4,708 patient-years for sitagliptin and 4 patients with an event in 3,942 patient-years for control) (see **PRECAUTIONS**, *Pancreatitis*).

Simvastatin

Simvastatin is generally well tolerated; for the most part adverse effects have been mild and transient in nature. In controlled clinical studies less than 2 percent of patients were discontinued due to adverse effects attributable to simvastatin.

The clinical adverse events occurring at an incidence of greater than 0.5% in controlled clinical trials and are considered to be definitely, probably or possibly due to simvastatin may be grouped as follows:

Adverse events	Simvastatin (%) (N=2,423)	Placebo (%) (N=167)
Body as a whole		
Abdominal pain	2.5	0.6
Asthenia	0.9	0.6
Digestive		
Constipation	2.5	1.2
Flatulence	2.0	0.6
Nausea	1.2	0.6
Acid regurgitation	0.6	0
Diarrhoea	0.8	0
Dyspepsia	0.7	0
Nervous System		
Headache	1.0	1.2
Insomnia	0.5	0
Dermatological		
Rash	0.7	0

Myopathy has been reported rarely (see **PRECAUTIONS**; *Myopathy/Rhabdomyolysis*).

In HPS (see **CLINICAL TRIALS**) involving 20,536 patients treated with 40 mg/day of simvastatin (n=10,269) or placebo (n=10,267), the safety profiles were comparable between patients treated with simvastatin and patients treated with placebo over the mean 5.3 years of the study. In this trial, only serious adverse effects and discontinuations due to any adverse effects were recorded. Discontinuation rates due to side effects were comparable (4.2% in patients treated with simvastatin compared with 4.3% in patients treated with placebo). The incidence of myopathy was 0.07% in patients treated with simvastatin compared with 0.03% in patients treated with placebo. This includes rhabdomyolysis for which incidences were 0.04% in patients treated with simvastatin compared with 0.01% in patients treated with placebo. Some of these patients were taking simvastatin concomitantly with medications which are known to increase the risk of myopathy (see **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*). Elevated transaminases (>3X ULN confirmed by repeat test) occurred in 0.21% of patients treated with simvastatin compared with 0.09% of patients treated with placebo.

In 4S (see **CLINICAL TRIALS**) involving 4,444 patients treated with 20-40 mg/day of simvastatin (n=2,221) or placebo (n=2,223), the safety and tolerability profiles were comparable between treatment groups over the median 5.4 years of the study.

Post-marketing Experience

Additional adverse reactions have been identified during post-marketing use of sitagliptin (as monotherapy and/or in combination with other antihyperglycaemic agents) or in clinical studies (other than those described above) or post-marketing use of simvastatin. Because the reactions listed below 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 exposure to sitagliptin or simvastatin.

Infections and infestations: upper respiratory tract infection; nasopharyngitis

Blood and lymphatic system disorders: anaemia

Psychiatric disorders: insomnia; depression

Nervous system disorders: headache; dizziness; paresthaesia; peripheral neuropathy;

Respiratory, thoracic and mediastinal disorders: interstitial lung disease

Gastrointestinal disorders: pancreatitis; acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see **PRECAUTIONS**, *Pancreatitis*); constipation; vomiting; nausea; diarrhoea; dyspepsia

Hepatobiliary disorders: hepatitis/jaundice; fatal and non-fatal hepatic failure

Skin and subcutaneous tissue disorders: rash; pruritus; alopecia

Musculoskeletal and connective tissue disorders: muscle cramps; myalgia; rhabdomyolysis; arthralgia; pain in extremity; back pain

Renal and urinary disorders: worsening renal function, including acute renal failure (sometimes requiring dialysis)

Reproductive system and breast disorders: erectile dysfunction, gynaecomastia

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions, including Stevens-Johnson syndrome have been reported with use of sitagliptin (see **CONTRAINDICATIONS**; **PRECAUTIONS**, *Hypersensitivity Reactions*).

Rhabdomyolysis and hepatitis/jaundice occurred rarely and hepatic failure occurred very rarely with simvastatin. An apparent hypersensitivity syndrome has been reported rarely with use of simvastatin which has included some of the following features: angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, eosinophilia, ESR increased, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, dyspnoea, and malaise.

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 non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

The following adverse effects have been reported; however, a causal relationship to therapy with simvastatin has not been established: erythema multiform including Stevens-Johnson syndrome, leucopenia, impotence, proteinuria**,** and purpura.

DOSAGE AND ADMINISTRATION

The recommended dose of JUVICOR are 100/10, 100/20, and 100/40 (mg sitagliptin/mg simvastatin) once daily as combination therapy with metformin, a sulfonylurea (clinical experience is with glimepiride as dual therapy), or a thiazolidinedione (clinical experience is with pioglitazone as dual therapy).

As patients with type 2 diabetes are considered to be at high risk of coronary events, the usual starting dose of JUVICOR for patients who are not already taking simvastatin is 100/40 mg/day given as a single dose in the evening. For patients already taking simvastatin (10-40 mg daily) with or without sitagliptin 100 mg daily, JUVICOR may be initiated at the dose of 100 mg sitagliptin and the dose of simvastatin already being taken. Pharmacotherapy can be initiated simultaneously with diet and exercise. JUVICOR can be taken with or without food, although co-administration with high-fat meals is not recommended (see **PHARMACOLOGY**, *Pharmacokinetics*).

Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 100/40 mg/day given as a single dose in the evening.

Advice to Patients Currently Taking Sitagliptin and/or Simvastatin

To prevent accidental excessive dosing due to inadvertent duplication of administration of sitagliptin and/or simvastatin, patients currently taking sitagliptin and/or simvastatin should be advised that JUVICOR replaces these medications and therefore the current sitagliptin and/or simvastatin medication(s) should no longer be taken. Patients should also be advised to take any remaining medication(s) to the pharmacy for appropriate disposal.

Concomitant Therapy

When JUVICOR is used in combination with a sulfonylurea, a lower dose of sulfonylurea may be considered to reduce the risk of sulfonylurea-induced hypoglycaemia (see **PRECAUTIONS**, *Hypoglycaemia in Combination with a Sulfonylurea*).

In patients taking fibrates other than gemfibrozil (see **CONTRAINDICATIONS**) or fenofibrate concomitantly with JUVICOR, the dose of JUVICOR should not exceed 100/10mg/day. In patients taking amiodarone, verapamil, or diltiazem concomitantly with JUVICOR, the dose of JUVICOR should not exceed 100/20 mg/day (see **PRECAUTIONS**, *Myopathy/Rhabdomyolysis*; **INTERACTIONS WITH OTHER MEDICINES**).

Patients with Renal Insufficiency

JUVICOR can be used in patients with normal renal function or mild renal insufficiency (creatinine clearance [CrCl] ≥50 mL/min, approximately corresponding to serum creatinine levels of ≤150 mmol/L in men and ≤133 mmol/L 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 insufficiency. JUVICOR is not recommended in patients with moderate or severe renal insufficiency (CrCl <50 mL/min, approximately corresponding to serum creatinine levels of >150 mmol/L in men and >133 mmol/L in women) or ESRD because doses of sitagliptin appropriate for patients with moderate or severe renal insufficiency or ESRD are not available in this combination product (see **PRECAUTIONS**, *Use in Patients with Renal Insufficiency*).

Assessment of renal function is recommended prior to initiation of JUVICOR and periodically thereafter. Creatinine clearance can be estimated from serum creatinine using the Cockcroft-Gault formula.

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 1.2}{[\text{serum creatinine (micromol/L)}]} \quad \{\times 0.85 \text{ for female patients}\}$$

Patients with Hepatic Insufficiency
JUVICOR is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases (see **CONTRAINDICATIONS**).

Patients with Homozygous Familial Hypercholesterolaemia
Based on the results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolaemia is 100/40 mg/day in the evening. JUVICOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 131 126 (in Australia) or 0800 764 766 (in New Zealand).

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 (e.g. liver function tests, electrocardiograms), and institute supportive therapy if required.

During controlled clinical trials in healthy subjects, single doses of up to 800 mg ***sitagliptin*** were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin (see **PHARMACOLOGY**, *Pharmacodynamics*). There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 400 mg per day for periods of up to 28 days. Sitagliptin is modestly dialysable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

A few cases of overdosage of ***simvastatin*** have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae.

PRESENTATION AND STORAGE CONDITIONS

JUVICOR 100/10 mg: is a pink-beige, round, bi-convex, film coated tablet, marked with "✪" and "753" on one side, and plain on the other side.

JUVICOR 100/20 mg: is a pink-beige, bi-convex, modified capsule shaped, film coated tablet, marked with "✪" and "757" on one side, and plain on the other side.

JUVICOR 100/40 mg: is an orange-beige, bi-convex, modified capsule shaped, film coated tablet, marked with "✪" and "773" on one side, and plain on the other side.

JUVICOR is available in aluminium blister packs of 28 film-coated tablets. JUVICOR is also available in starter packs of 7 tablets.

Both sitagliptin and simvastatin are also contained in XELEZOR and TESOZOR fixed combination tablets.

Store below 30°C. Store in original container.

NAME AND ADDRESS OF THE SPONSOR
Merck Sharp & Dohme (Australia) Pty Limited
54-68 Ferndell Street
South Granville NSW 2142

POISON SCHEDULE OF THE MEDICINE: Prescription only medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 05 December 2012

DATE OF MOST RECENT AMENDMENT: N/A