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PRODUCT CIRCULAR

SITAGLIPTIN

XELEVIA®

Film-Coated Tablet

Dipeptidyl Peptidase-4 Inhibitor

Rx

NAME AND STRENGTH OF ACTIVE INGREDIENTS

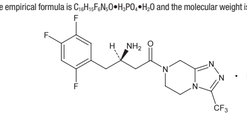
Each film-coated tablet of SITAGLIPTIN (XELEVIA) contains 64.25, or 128.5 mg of sitagliptin phosphate monohydrate, which is equivalent to 50, or 100 mg, respectively, of free base.

PRODUCT DESCRIPTION

SITAGLIPTIN (XELEVIA) is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme for the treatment of type 2 diabetes. 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 physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. 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 hypoglycemia in patients with type 2 diabetes and in normal subjects. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and 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 ($PPAR\gamma$) agonists, alpha-glucosidase inhibitors, and amylin analogues.

SITAGLIPTIN (XELEVIA) tablets contain sitagliptin phosphate, an orally-active, potent, and selective inhibitor of dipeptidyl peptidase-4 (DPP-4), which 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:



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.

PHARMACOKINETICS

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

Absorption

The absolute bioavailability of sitagliptin is approximately 87%. Since co-administration of a high-fat meal with SITAGLIPTIN (XELEVIA) had no effect on the pharmacokinetics, SITAGLIPTIN (XELEVIA) may be administered with or without food.

Distribution

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

Metabolism

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79% of sitagliptin is excreted unchanged in the urine.

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

Elimination

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

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

Characteristics in Patients

Renal Impairment: A single-dose, open-label study was conducted to evaluate the pharmacokinetics of SITAGLIPTIN (XELEVIA) (50 mg dose) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on hemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (eGFR ≥ 60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2) and patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2 to < 45 mL/min/1.73 m^2), and approximately 4-fold in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), including patients with ESRD on hemodialysis. Sitagliptin was modestly removed by hemodialysis (13.5% over a 3- to 4-hour hemodialysis session starting 4 hours postdose). To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with eGFR <45 mL/min/1.73 m^2. (See **RECOMMENDED DOSE**, *Patients with Renal Impairment*.)

Hepatic Impairment: In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100 mg dose of SITAGLIPTIN (XELEVIA). These differences are not considered to be clinically meaningful. No dosage adjustment for SITAGLIPTIN (XELEVIA) is necessary for patients with mild or moderate hepatic impairment.

There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score >9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

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Elderly: No dosage adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

Pediatric:

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in pediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference based on the flat PK/PD relationship between the dose of 50 mg and 100 mg in adults.

No studies with sitagliptin have been performed in pediatric patients < 10 years of age.

Gender: No dosage adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Race: No dosage adjustment is necessary based on race. Race had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data, including subjects of white, Hispanic, black, Asian, and other racial groups.

Body Mass Index (BMI): No dosage adjustment is necessary based on BMI. Body mass index had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

Type 2 Diabetes: The pharmacokinetics of sitagliptin in patients with type 2 diabetes are generally similar to those in healthy subjects.

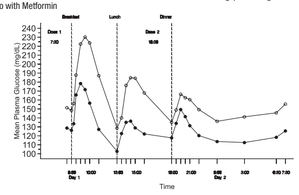
PHARMACODYNAMICS

General

In patients with type 2 diabetes, administration of single oral doses of SITAGLIPTIN (XELEVIA) 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 (XELEVIA) 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.

In Phase II studies, SITAGLIPTIN (XELEVIA) 50 mg twice daily provided no additional glycemic efficacy compared to 100 mg once daily.

In a randomized, placebo-controlled, double-blind, double-dummy, four-period crossover study in healthy adult subjects, the effects on post-meal plasma concentrations of active and total GLP-1 and glucose after co-administration of sitagliptin and metformin were compared with those after administration of sitagliptin alone, metformin alone, or placebo, each administered for two days. The incremental 4-hour post-meal weighted mean active GLP-1 concentrations were increased by approximately 2-fold after either administration of sitagliptin alone or metformin alone compared with placebo. The effect on active GLP-1 concentrations after co-administration of sitagliptin and metformin were additive, with active GLP-1 concentrations increased by approximately 4-fold compared with placebo. Sitagliptin alone increased only active GLP-1 concentrations, reflecting inhibition of DPP-4, whereas metformin alone increased active and total GLP-1 concentrations to a similar extent. These data are consistent with different mechanisms for the increase in active GLP-1 concentrations. Results from the study also demonstrated that sitagliptin, but not metformin, enhances active GIP concentrations.

In studies with healthy subjects, SITAGLIPTIN (XELEVIA) did not lower blood glucose or cause hypoglycemia, suggesting that the insulinotropic and glucagon suppressive actions of the drug are glucose dependent.

Effects on blood pressure

In a randomized, placebo-controlled crossover study in hypertensive patients on one or more anti-hypertensive drugs (including angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, calcium-channel blockers, beta-blockers and diuretics), co-administration with SITAGLIPTIN (XELEVIA) was generally well tolerated. In these patients, SITAGLIPTIN (XELEVIA) had a modest blood pressure lowering effect; 100 mg per day of SITAGLIPTIN (XELEVIA) 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 randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of SITAGLIPTIN (XELEVIA) 100 mg, SITAGLIPTIN (XELEVIA) 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 postdose 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 (XELEVIA) 100 mg (N=81) or SITAGLIPTIN (XELEVIA) 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.

INDICATIONS

Monotherapy

SITAGLIPTIN (XELEVIA) is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Combination with Metformin

SITAGLIPTIN (XELEVIA) is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin as initial therapy or when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Combination with a Sulfonylurea

SITAGLIPTIN (XELEVIA) is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a sulfonylurea when treatment with the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Combination with a PPARγ agonist

SITAGLIPTIN (XELEVIA) is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with a $PPAR\gamma$ agonist (i.e., thiazolidinediones) as initial therapy or when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Combination with Metformin and a Sulfonylurea

SITAGLIPTIN (XELEVIA) is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.

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Combination with Metformin and a PPARγ agonist

SITAGLIPTIN (XELEVIA) is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a $PPAR\gamma$ agonist (i.e., thiazolidinediones) when dual therapy with these agents, with diet and exercise, does not provide adequate glycemic control.

Combination with Insulin

SITAGLIPTIN (XELEVIA) is indicated in patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in combination with insulin (with or without metformin).

RECOMMENDED DOSE

The recommended dose of SITAGLIPTIN (XELEVIA) is 100 mg once daily as monotherapy or as combination therapy with metformin, a sulfonylurea, insulin (with or without metformin), a $PPAR\gamma$ agonist (e.g., thiazolidinediones), metformin plus a sulfonylurea, or metformin plus a $PPAR\gamma$ agonist.

When SITAGLIPTIN (XELEVIA) is used in combination with a sulfonylurea or with insulin, a lower dose of sulfonylurea or insulin may be considered to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia. (See **WARNINGS AND PRECAUTIONS,** *Hypoglycemia in Combination with a Sulfonylurea or with Insulin*.)

Patients with Renal Impairment

Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of SITAGLIPTIN (XELEVIA) and periodically thereafter.

For patients with mild renal impairment (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2 to < 90 mL/min/1.73 m^2), no dosage adjustment for SITAGLIPTIN (XELEVIA) is required.

For patients with moderate renal impairment (eGFR ≥ 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2), no dosage adjustment for SITAGLIPTIN (XELEVIA) is required.

For patients with moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2 to <45 mL/min/1.73 m^2), the dose of SITAGLIPTIN (XELEVIA is 50 mg once daily.

For patients with severe renal impairment (eGFR ≥ 15 mL/min/1.73 m^2 to < 30 mL/min/1.73 m^2) or with end-stage renal disease (ESRD) (eGFR < 15 mL/min/1.73 m^2), including those requiring hemodialysis or peritoneal dialysis, the dose of SITAGLIPTIN (XELEVIA) is 25 mg once daily. SITAGLIPTIN (XELEVIA) may be administered without regard to the timing of dialysis.

MODE OF ADMINISTRATION

SITAGLIPTIN (XELEVIA) can be taken orally with or without food.

CONTRAINDICATIONS

SITAGLIPTIN (XELEVIA) is contraindicated in patients who are hypersensitive to any components of this product. (See **WARNINGS AND PRECAUTIONS**, *Hypersensitivity Reactions* and **UNDESIRABLE EFFECTS**, *Postmarketing Experience*.)

WARNINGS AND PRECAUTIONS

General

SITAGLIPTIN (XELEVIA) should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Pancreatitis: There have been reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis (see **UNDESIRABLE EFFECTS**), in patients taking sitagliptin. 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, SITAGLIPTIN (XELEVIA) and other potentially suspect medicinal products should be discontinued.

Use in Patients with Renal Impairment: SITAGLIPTIN (XELEVIA) is renally excreted. To achieve plasma concentrations of SITAGLIPTIN (XELEVIA) similar to those in patients with normal renal function, lower dosages are recommended in patients with eGFR <45 mL/min/1.73 m^2, as well as in ESRD patients requiring hemodialysis or peritoneal dialysis. (See **RECOMMENDED DOSE**, *Patients with Renal Impairment*.)

Hypoglycemia in Combination with a Sulfonylurea or with Insulin: In clinical trials of SITAGLIPTIN (XELEVIA) as monotherapy and as part of combination therapy with agents not known to cause hypoglycemia (i.e. metformin or a $PPAR\gamma$ agonist (thiazolidinedione), rates of hypoglycemia reported with SITAGLIPTIN (XELEVIA) were similar to rates in patients taking placebo. As is typical with other antihyperglycemic agents, hypoglycemia has been observed when SITAGLIPTIN (XELEVIA) was used in combination with insulin or a sulfonylurea (see **UNDESIRABLE EFFECTS**). Therefore, to reduce the risk of sulfonylurea- or insulin-induced hypoglycemia, a lower dose of sulfonylurea or insulin may be considered (see **RECOMMENDED DOSE**).

Hypersensitivity Reactions: There have been postmarketing reports of serious hypersensitivity reactions in patients treated with SITAGLIPTIN (XELEVIA). 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 drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with SITAGLIPTIN (XELEVIA), with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue SITAGLIPTIN (XELEVIA), assess for other potential causes for the event, and institute alternative treatment for diabetes. (See **CONTRAINDICATIONS** and **UNDESIRABLE EFFECTS**, *Postmarketing Experience*.)

Bullous Pemphigoid: Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving SITAGLIPTIN (XELEVIA). If bullous pemphigoid is suspected, SITAGLIPTIN (XELEVIA) should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

INTERACTIONS WITH OTHER MEDICAMENTS

In drug interaction studies, sitagliptin did not have clinically meaningful effects on the pharmacokinetics of the following: metformin, rosiglitazone, glyburide, simvastatin, warfarin, and oral contraceptives. Based on these data, sitagliptin does not inhibit CYP isozymes CYP3A4, 2C8, or 2C9. Based on *in vitro* data, sitagliptin is also not expected to inhibit CYP2D6, 1A2, 2C19 or 2B6 or to induce CYP3A4.

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.

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 cholesterol-lowering agents (e.g., statins, fibrates, ezetimibe), anti-platelet agents (e.g., clopidogrel), antihypertensives (e.g., ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydrochlorothiazide), analgesics and non-steroidal anti-inflammatory agents (e.g., naproxen, diclofenac, celecoxib), anti-depressants (e.g., bupropion, fluoxetine, sertraline), antihistamines (e.g., cetirizine), proton-pump inhibitors (e.g., omeprazole, lansoprazole), and medications for erectile dysfunction (e.g., sildenafil).

There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C_{max}, 18%) of digoxin with the co-administration of sitagliptin. These increases are not considered to be clinically meaningful. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or SITAGLIPTIN (XELEVIA) is recommended.

The AUC and C_{max} of sitagliptin were increased approximately 29% and 68%, respectively, in subjects with co-administration of a single 100-mg oral dose of SITAGLIPTIN (XELEVIA) and a single 600-mg oral dose of cyclosporine, a potent probe inhibitor of p-glycoprotein. The observed changes in sitagliptin pharmacokinetics are not considered to be clinically meaningful. No dosage adjustment for SITAGLIPTIN (XELEVIA) is recommended when co-administered with cyclosporine or other p-glycoprotein inhibitors (e.g., ketoconazole).

PREGNANCY AND LACTATION

Sitagliptin was not teratogenic in rats at oral doses up to 250 mg/kg or in rabbits given up to 125 mg/kg during organogenesis (up to 32 and 22 times, respectively, the human exposure based on the recommended daily adult human dose of 100 mg/day). In rats, a slight increase in the incidence of fetal rib malformations (absent, hypoplastic and wavy ribs) was observed at oral doses of 1000 mg/kg/day (approximately 100 times the human exposure based on the recommended daily adult human dose of 100 mg/day). Slight decreases in mean preweaning body weights of both sexes and postweaning body weight gains of males were observed in the offspring of rats given oral dose of 1000 mg/kg/day. However, animal reproduction studies are not always predictive of the human response.

There are no adequate and well-controlled studies in pregnant women; therefore, the safety of SITAGLIPTIN (XELEVIA) in pregnant women is not known. SITAGLIPTIN (XELEVIA), like other oral antihyperglycemic agents, is not recommended for use in pregnancy.

Sitagliptin is secreted in the milk of lactating rats. It is not known whether sitagliptin is secreted in human milk. Therefore, SITAGLIPTIN (XELEVIA) should not be used by a woman who is nursing.

PEDIATRIC USE

A 54-week, double-blind study was conducted to evaluate the efficacy and safety of SITAGLIPTIN (XELEVIA) in pediatric patients (10 to 17 years of age) with type 2 diabetes who were not on anti-hyperglycaemic therapy for at least 12 weeks or were on a stable dose of insulin for at least 12 weeks. Patients were randomized and treated with SITAGLIPTIN (XELEVIA) 100 mg (N=95) or placebo (N=95) once daily for 20 weeks.

Treatment with SITAGLIPTIN (XELEVIA) 100 mg did not provide significant improvement in HbA_{1c} at 20 weeks.

In pediatric patients aged 10 to 17 years with type 2 diabetes, the profile of side effects was comparable to that observed in adults.

SITAGLIPTIN (XELEVIA) has not been studied in pediatric patients under 10 years of age.

USE IN THE ELDERLY

In clinical studies, the safety and effectiveness of SITAGLIPTIN (XELEVIA) in the elderly (≥65 years) were comparable to those seen in younger patients (<65 years). No dosage adjustment is required based on age. Elderly patients are more likely to have renal impairment; as with other patients, dosage adjustment may be required in the presence of significant renal impairment (see **RECOMMENDED DOSE**, *Patients with Renal Impairment*).

UNDESIRABLE EFFECTS

SITAGLIPTIN (XELEVIA) was generally well tolerated in controlled clinical studies as both monotherapy and combination therapy, with discontinuation of therapy due to clinical adverse experiences similar to placebo.

In four placebo-controlled clinical studies as both monotherapy (one study of 18- and one of 24-week duration) and add-on combination therapy with metformin or pioglitazone (both of 24-week duration), there were 1082 patients treated with SITAGLIPTIN (XELEVIA) 100 mg once daily and 778 patients given placebo. (Two of these studies also included 456 patients treated with SITAGLIPTIN (XELEVIA) 200 mg daily, two times the recommended daily dose.) There were no drug-related adverse reactions reported that occurred with an incidence of ≥1% in patients receiving SITAGLIPTIN (XELEVIA) 100 mg. Overall, the safety profile of the 200-mg daily dose was similar to that of the 100-mg daily dose.

In a prespecified pooled analysis of the above studies, the overall incidence of adverse experiences of hypoglycemia in patients treated with SITAGLIPTIN (XELEVIA) 100 mg was similar to placebo (1.2% vs. 0.9%). The incidences of selected gastrointestinal adverse experiences in patients treated with SITAGLIPTIN (XELEVIA) or placebo were: abdominal pain [SITAGLIPTIN (XELEVIA), 2.3%; placebo, 2.1%], nausea (1.4%, 0.6%), vomiting (0.8%, 0.9%), and diarrhea (3.0%, 2.3%).

In all studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required.

Add-on Combination with a Sulfonylurea: In a 24-week placebo-controlled study of SITAGLIPTIN (XELEVIA) 100 mg in combination with glimepiride or with glimepiride and metformin [SITAGLIPTIN (XELEVIA), N=222; placebo, N=219], the drug-related adverse reaction reported in ≥1% of patients treated with SITAGLIPTIN (XELEVIA) and more commonly than in patients treated with placebo was hypoglycemia [SITAGLIPTIN (XELEVIA), 9.5%; placebo, 0.9%].

Add-on Combination with Metformin and a PPARγ Agonist: In a placebo-controlled study of SITAGLIPTIN (XELEVIA) 100 mg in combination with metformin and rosiglitazone [SITAGLIPTIN (XELEVIA), N=170; placebo, N=92], the drug-related adverse reactions reported through the primary time point at Week 18 in ≥1% of patients treated with SITAGLIPTIN (XELEVIA) and more commonly than in patients treated with placebo were: headache [SITAGLIPTIN (XELEVIA), 2.4%; placebo, 0.0%], diarrhea (1.8%, 1.1%), nausea (1.2%, 1.1%), hypoglycemia (1.2%, 0.0%), and vomiting (1.2%, 0.0%). Through Week 54, the drug-related adverse reactions reported in ≥1% of patients treated with SITAGLIPTIN (XELEVIA) and more commonly than in patients treated with placebo were: headache (2.4%, 0.0%), hypoglycemia (2.4%, 0.0%), upper respiratory tract infection (1.8%, 0.0%), nausea (1.2%, 1.1%), cough (1.2%, 0.0%), fungal skin infection (1.2%, 0.0%), peripheral edema (1.2%, 0.0%), and vomiting (1.2%, 0.0%).

Initial Combination Therapy with Metformin: In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 100 mg in combination with metformin at 1000 mg or 2000 mg per day (administered as sitagliptin 50 mg/metformin 500 mg or 1000 mg twice daily), the drug-related adverse reactions reported in ≥1% of patients treated with sitagliptin plus metformin (N=372) and more commonly than in patients treated with metformin alone (N=364) were: diarrhea (sitagliptin plus metformin, 3.5%; metformin, 3.3%), dyspepsia (1.3%; 1.1%), flatulence (1.3%; 0.5%), vomiting (1.1%; 0.3%), and headache (1.3%; 1.1%). The incidence of hypoglycemia was 1.1% in patients given sitagliptin in combination with metformin and 0.5% in patients given metformin alone.

Initial Combination Therapy with a PPARγ Agonist: In a 24-week study of initial therapy with SITAGLIPTIN (XELEVIA) at 100 mg/day in combination with pioglitazone at 30 mg/day, the only drug-related adverse reaction reported in ≥1% of patients treated with SITAGLIPTIN (XELEVIA) with pioglitazone (N=261) and more commonly than in patients treated with pioglitazone alone (N=259) was (asymptomatic) decreased blood glucose [SITAGLIPTIN (XELEVIA) with pioglitazone, 1.1%; pioglitazone, 0.0%]. The incidence of (symptomatic) hypoglycemia was 0.4% in patients given SITAGLIPTIN (XELEVIA) in combination with pioglitazone and 0.8% in patients given pioglitazone.

Add-on Combination with Insulin: In a 24-week placebo-controlled study of SITAGLIPTIN (XELEVIA) 100 mg in combination with stable-dose insulin (with or without metformin), the drug-related adverse reactions reported in ≥1% of patients treated with SITAGLIPTIN (XELEVIA) (N=322) and more commonly than in patients treated with placebo (N=319) were: hypoglycemia [SITAGLIPTIN (XELEVIA), 9.6%; placebo, 5.3%], influenza (1.2%, 0.3%), and headache (1.2%, 0.0%). In another 24-week study of patients receiving SITAGLIPTIN (XELEVIA) as add-on therapy while undergoing insulin intensification (with or without metformin), there were no drug-related adverse reactions reported that occurred with an incidence of ≥1% in patients treated with SITAGLIPTIN (XELEVIA) 100 mg and more commonly than in patients treated with placebo.

Pancreatitis: In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of non-adjudicated acute pancreatitis events was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for sitagliptin and 4 patients with an event in 3942 patient-years for control). See also *TECOS Cardiovascular Safety Study*, below. (See **WARNINGS AND PRECAUTIONS**, *Pancreatitis*).

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

TECOS Cardiovascular Safety Study: The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with SITAGLIPTIN (XELEVIA), 100 mg daily (or 50 mg daily if the baseline estimated glomerular filtration rate (eGFR) was ≥30 and <50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA_{1c} and CV risk factors. The study population included a total of 2,004 patients ≥75 years of age [970 treated with SITAGLIPTIN (XELEVIA) and 1,034 treated with placebo]. The overall incidence of serious adverse events in patients receiving SITAGLIPTIN (XELEVIA) was similar to that in patients receiving placebo. Assessment of pre-specified diabetes-related complications revealed similar incidences between groups including infections [18.4% of the SITAGLIPTIN (XELEVIA)-treated patients and 17.7% of the placebo-treated patients] and renal failure [1.4% of SITAGLIPTIN (XELEVIA)-treated patients and 1.5% of placebo-treated patients]. The adverse event profile in patients ≥75 years of age was generally similar to the overall population.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 2.7% in SITAGLIPTIN (XELEVIA)-treated patients and 2.5% in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycemia was 1.0% in SITAGLIPTIN (XELEVIA)-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in SITAGLIPTIN (XELEVIA)-treated patients and 0.2% in placebo-treated patients. The incidence of adjudication-confirmed malignancy events was 3.7% in SITAGLIPTIN (XELEVIA)-treated patients and 4.0% in placebo-treated patients.

Pediatric population: In a clinical study with SITAGLIPTIN (XELEVIA) 100 mg in pediatric patients aged 10 to 17 years with type 2 diabetes, there were no drug-related adverse reactions reported through the 54-week treatment period in more than 1 patient in the SITAGLIPTIN (XELEVIA) group (N=95) and more commonly than in patients in the placebo group (N=90).

There were no clinically relevant differences between the SITAGLIPTIN (XELEVIA) and placebo groups through Week 54 in laboratory safety endpoints, vital signs, indices of adiposity, or growth and development endpoints.

Postmarketing Experience:

Additional adverse reactions have been identified during postmarketing use of SITAGLIPTIN (XELEVIA) as monotherapy and/or in combination with other antihyperglycemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions, including Stevens-Johnson syndrome (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**, *Hypersensitivity Reactions*); acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis (see **WARNINGS AND PRECAUTIONS**, *Pancreatitis*); worsening renal function, including acute renal failure (sometimes requiring dialysis); bullous pemphigoid (see **WARNINGS AND PRECAUTIONS**, Bullous Pemphigoid); upper respiratory tract infection; nasopharyngitis; constipation; vomiting; headache; arthralgia; myalgia; pain in extremity; back pain, pruritus.

Laboratory Test Findings

The incidence of laboratory adverse experiences was similar in patients treated with SITAGLIPTIN (XELEVIA) 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 6600 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.

OVERDOSAGE

During controlled clinical trials in healthy subjects, single doses of up to 800 mg SITAGLIPTIN (XELEVIA) 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 (XELEVIA) (see **PHARMACODYNAMICS**, ***Cardiac Electrophysiology***). 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 (XELEVIA) with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

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

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

DOSAGE FORM AND PACKAGING AVAILABLE

Each film-coated SITAGLIPTIN (XELEVIA) 50 mg Tablet contains 64.25 mg sitagliptin, which is equivalent to 50 mg of free base, available in PVDC/PE/PVC white blisters x 7's, box of 28's.
Each film-coated SITAGLIPTIN (XELEVIA) 100 mg Tablet contains 128.5 mg sitagliptin, which is equivalent to 100 mg of free base, available in PVDC/PE/PVC white blisters x 7's, box of 28's.

CAUTION

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DATE OF REVISION OF PACKAGE INSERT

June 2022

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Registration numbers:
Sitagliptin (XELEVIA®) 50 mg Film-Coated Tablet: DRP-5945-01
Sitagliptin (XELEVIA®) 100 mg Film-Coated Tablet: DRP-5944-01

Date of First Authorization: June 22, 2012

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000025676-PH

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Imported by:
MERCK SHARP & DOHME (I.A.) LLC
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Distributed by:
ESSEX PHARMACEUTICALS, INC.
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Makati City, Metro Manila, Philippines

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Worldwide Patient Product Information (WPPI)
INFORMATION FOR THE PATIENT ABOUT

SITAGLIPTIN
XELEVIA®
Film-Coated Tablet
Dipeptidyl Peptidase-4 Inhibitor

℞

Please read this information carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information may have changed.
Remember that your doctor has prescribed this medicine only for you. Never give it to anyone else.

What is SITAGLIPTIN (XELEVIA)?

SITAGLIPTIN (XELEVIA) is a tablet that contains 50 or 100 mg of sitagliptin as the active ingredient.

SITAGLIPTIN (XELEVIA) is a member of a class of medicines you take by mouth called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors) that lowers blood sugar levels in patients with type 2 diabetes mellitus. Type 2 diabetes is also called non-insulin-dependent diabetes mellitus, or NIDDM.

- SITAGLIPTIN (XELEVIA) helps to improve the levels of insulin after a meal.
- SITAGLIPTIN (XELEVIA) decreases the amount of sugar made by the body.
- SITAGLIPTIN (XELEVIA) works when blood sugar is high, especially after a meal. This is when the body needs the greatest amount of help in lowering blood sugar. SITAGLIPTIN (XELEVIA) also lowers blood sugar between meals.
- SITAGLIPTIN (XELEVIA) by itself is unlikely to cause low blood sugar (hypoglycemia) because it does not work when your blood sugar is low.

Why has my doctor prescribed SITAGLIPTIN (XELEVIA)?

Your doctor has prescribed SITAGLIPTIN (XELEVIA) to help lower your blood sugar, which is too high because of your type 2 diabetes. SITAGLIPTIN (XELEVIA) can be used alone or in combination with certain other medicines that lower blood sugar, along with a recommended diet and exercise program.

What is type 2 diabetes?

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

The main goal of treating diabetes is to lower your blood sugar to a normal level. Lowering and controlling blood sugar may help prevent or delay complications of diabetes, such as heart disease, kidney disease, blindness, and amputation.

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

What should I know before and while taking SITAGLIPTIN (XELEVIA)?

Who should not take SITAGLIPTIN (XELEVIA)?

Do not take SITAGLIPTIN (XELEVIA) if you are allergic to any of the ingredients in SITAGLIPTIN (XELEVIA).

What should I tell my doctor before taking SITAGLIPTIN (XELEVIA)?

Tell your doctor if you have or have had:

- type 1 diabetes
- diabetic ketoacidosis (increased ketones in the blood or urine)
- any kidney problems, or any past or present medical problems
- an allergic reaction to SITAGLIPTIN (XELEVIA)

While taking SITAGLIPTIN (XELEVIA)

Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving SITAGLIPTIN (XELEVIA). Pancreatitis can be a serious, potentially life-threatening medical condition. Stop taking SITAGLIPTIN (XELEVIA) and call your doctor if you experience severe and persistent stomach pain, with or without vomiting, because you could have pancreatitis.

Cases of a skin reaction called bullous pemphigoid that can require treatment in a hospital have been reported in patients receiving SITAGLIPTIN (XELEVIA). Tell your doctor if you develop blisters or the breakdown of your skin (erosion). Your doctor may tell you to stop taking SITAGLIPTIN (XELEVIA).

Use in children

SITAGLIPTIN (XELEVIA) is not effective in children and adolescents 10 to 17 years of age with type 2 diabetes. SITAGLIPTIN (XELEVIA) has not been studied in children younger than 10 years of age.

Use in the elderly

In studies, SITAGLIPTIN (XELEVIA) worked well in and was well-tolerated by older adult patients. No dosage adjustment is necessary based on age.

Use in pregnancy and breast-feeding

Women who are pregnant or plan to become pregnant should consult with their doctor before taking SITAGLIPTIN (XELEVIA). SITAGLIPTIN (XELEVIA) is not recommended for use during pregnancy.

It is not known if SITAGLIPTIN (XELEVIA) passes into breast milk. You should not use SITAGLIPTIN (XELEVIA) if you are breast-feeding or plan to breast-feed.

Can I take SITAGLIPTIN (XELEVIA) with other medicines?

SITAGLIPTIN (XELEVIA) may be taken with most medicines. Tell your doctor about all the medicines you take. This includes prescription and non-prescription medicines, and herbal supplements.

Can I drive or operate machinery while using SITAGLIPTIN (XELEVIA)?

There is no information to suggest that SITAGLIPTIN (XELEVIA) affects your ability to drive a car or operate machinery.

How should I take SITAGLIPTIN (XELEVIA)?

Take SITAGLIPTIN (XELEVIA) exactly as your doctor has prescribed. The recommended dose is to take:

- one 100 mg tablet
- once a day
- by mouth, with or without food

If you have kidney problems, your doctor may prescribe lower doses.

Your doctor may prescribe SITAGLIPTIN (XELEVIA) along with certain other medicines that lower blood sugar.

Continue to take SITAGLIPTIN (XELEVIA) as long as your doctor prescribes it so you can continue to help control your blood sugar.

Diet and exercise can help your body use its blood sugar better. It is important to stay on your doctor recommended diet, exercise and weight loss program while taking SITAGLIPTIN (XELEVIA).

What should I do in case of an overdose?

If you take more than the prescribed dosage of SITAGLIPTIN (XELEVIA), contact your doctor immediately.

What should I do if I miss a dose?

If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of SITAGLIPTIN (XELEVIA).

What undesirable effects may SITAGLIPTIN (XELEVIA) have?

Like all prescription medicines, SITAGLIPTIN (XELEVIA) may cause side effects. In studies, side effects usually were mild and did not cause patients to stop taking SITAGLIPTIN (XELEVIA). The side effects reported in patients treated with SITAGLIPTIN (XELEVIA) were similar to side effects in patients treated with a tablet containing no medication (a placebo).

When SITAGLIPTIN (XELEVIA) is used in combination with a sulfonylurea medicine or with insulin, low blood sugar with symptoms (hypoglycemia) due to the sulfonylurea or insulin can occur. Lower doses of the sulfonylurea medicine or insulin may be required.

When SITAGLIPTIN (XELEVIA) was used in combination with insulin, the following additional side effects were reported:

- Flu
- Headache

When SITAGLIPTIN (XELEVIA) and metformin were started together, the following side effects were reported:

- Diarrhea
- Indigestion
- Flatulence
- Vomiting
- Headache

When SITAGLIPTIN (XELEVIA) and pioglitazone were started together, the side effect of decreased blood sugar measurements without symptoms of hypoglycemia was reported.

When SITAGLIPTIN (XELEVIA) was used in combination with metformin and rosiglitazone, the following side effects were reported:

- Headache
- Low blood sugar with symptoms (hypoglycemia)
- Diarrhea
- Upper respiratory infection
- Nausea
- Cough
- Fungal skin infection
- Swelling of the hands or legs
- Vomiting

Additional side effects have been reported in general use with SITAGLIPTIN (XELEVIA), by itself and/or with other diabetes medicines:

- Allergic reactions, which may be serious, including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing. If you have an allergic reaction, stop taking SITAGLIPTIN (XELEVIA) and call your doctor right away. Your doctor may prescribe a medication to treat your allergic reaction and a different medication for your diabetes
- Inflammation of the pancreas
- Kidney problems (sometimes requiring dialysis)
- Upper respiratory infection
- Shuffy or runny nose and sore throat
- Constipation
- Vomiting
- Headache
- Joint pain
- Muscle aches
- Arm or leg pain
- Back pain
- Itching
- Blisters

Tell your doctor or pharmacist if you develop any unusual side effect, or if any known side effect does not go away or gets worse.

How can I learn more about SITAGLIPTIN (XELEVIA) and diabetes?

You may obtain further information from your doctor or pharmacist, who has more detailed information.

How long should I keep my medicine?

Do not use this medicine after the month and year shown by the four numbers following EX (or EXP) on the container. The first two numbers indicate the month; the last two numbers indicate the year.

How should I store SITAGLIPTIN (XELEVIA)?

Store at temperatures not exceeding 30°C.
Keep SITAGLIPTIN (XELEVIA) and all medicines safely away from children.

DOSAGE FORM AND PACKAGING AVAILABLE

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