WPC-MK0431A-T-062022
000025681-PH

PRODUCT CIRCULAR

SITAGLIPTIN METFORMIN HCl

VELMETIA®

Film-Coated Tablets
Antidiabetic

Rx

NAME AND STRENGTH OF ACTIVE INGREDIENTS

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is available for oral administration as tablets containing 64.25 mg sitagliptin phosphate monohydrate equivalent to: 50 mg sitagliptin as free base and 500 mg metformin hydrochloride [SITAGLIPTIN + METFORMIN HCl (VELMETIA) 50 mg/500 mg] or 1 g metformin hydrochloride [SITAGLIPTIN + METFORMIN HCl (VELMETIA) 50 mg/1 g].

PRODUCT DESCRIPTION

SITAGLIPTIN + METFORMIN HCl (VELMETIA)

SITAGLIPTIN + METFORMIN HCl (VELMETIA) combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Sitagliptin phosphate

Sitagliptin phosphate 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 (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

Metformin hydrochloride

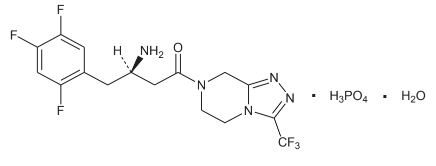
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **WARNINGS AND PRECAUTIONS**, *Metformin hydrochloride*) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) contains sitagliptin phosphate and metformin hydrochloride.

Sitagliptin phosphate

The chemical name of sitagliptin phosphate is 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.

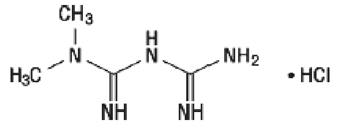
The empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and the molecular weight is 523.32. The structural formula is:



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.

Metformin hydrochloride

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula is as shown:



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot HCl$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether and chloroform. The pK_a of metformin is 12.4. The pH of a 1 % aqueous solution of metformin hydrochloride is 6.68.

PHARMACOKINETICS

SITAGLIPTIN + METFORMIN HCl (VELMETIA)

The results of a definitive bioequivalence study in healthy subjects demonstrated that the SITAGLIPTIN + METFORMIN HCl (VELMETIA) 50 mg/500 mg and 50 mg/1 g combination tablets are bioequivalent to co-administration of corresponding doses of SITAGLIPTIN (JANUVIA®) and metformin hydrochloride as individual tablets.

Because bioequivalence is demonstrated at the lowest and highest combination tablet dose strengths available, bioequivalence is conferred to the (sitagliptin/metformin) 50 mg/850 mg fixed dose combination (FDC) tablet.

Absorption

Sitagliptin phosphate

The absolute bioavailability of sitagliptin is approximately 87 %. Co-administration of a high-fat meal with sitagliptin phosphate had no effect on the pharmacokinetics of sitagliptin.

Metformin hydrochloride

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alternation in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35-minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850-mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Sitagliptin phosphate

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%).

Metformin hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride tablets, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally < 1 mcg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 mcg/mL, even at maximum doses.

Metabolism

Sitagliptin phosphate

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.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

Elimination

Sitagliptin phosphate

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.

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Characteristics in Patients

Type 2 Diabetes

Sitagliptin phosphate

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

Metformin hydrochloride

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.

Renal Impairment

Sitagliptin phosphate

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to < 45 mL/min/1.73 m², and an approximately 4-fold increase was observed in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²) including patients with end-stage renal disease (ESRD) on hemodialysis, as compared to subjects with normal renal function.

Metformin hydrochloride

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Hepatic Impairment

Sitagliptin phosphate

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 phosphate. These differences are not considered to be clinically meaningful.

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.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Gender

Sitagliptin phosphate

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.

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender. Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Elderly

Sitagliptin phosphate

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.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see **GLUCOPHAGE**[1] prescribing information: **CLINICAL PHARMACOLOGY**, Special Populations, Geriatrics).

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.

Race

Sitagliptin phosphate

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.

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n= 51), and Hispanics (n=24).

Body Mass Index (BMI)

Sitagliptin phosphate

Body mass index (BMI) 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.

PHARMACODYNAMICS

Sitagliptin phosphate

General

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 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. In Phase II studies, sitagliptin 50 mg twice daily provided similar glycemic efficacy compared to sitagliptin 100 mg once daily.

In a randomized, placebo-controlled, double-blind, double-dummy, four-period crossover two-day 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 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 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 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 randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the recommended dose), and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any other time during the study. Following the 800-mg dose, the maximum increase in the placebo-corrected mean change in QTc from baseline 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 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.

[1] **GLUCOPHAGE®** is a registered trademark of Merck Sante S.A.S, an associate of Merck KGaA of Darmstadt, Germany.
Licensed to Bristol-Meyers Squibb Company.

INDICATIONS

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is indicated as initial therapy in patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise do not provide adequate glycemic control.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus inadequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is indicated as part of triple combination therapy with a sulfonylurea as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a sulfonylurea.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is indicated as part of triple combination therapy with a PPARγ agonist (i.e., thiazolidinediones) as an adjunct to diet and exercise in patients with type 2 diabetes mellitus inadequately controlled with any two of the three agents: metformin, sitagliptin, or a PPARγ agonist.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is indicated in patients with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control in combination with insulin.

RECOMMENDED DOSE

General

The dosage of antihyperglycemic therapy with SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) should generally be given twice daily with meals, with gradual dose escalation, to reduce the gastrointestinal (GI) side effects associated with metformin.

Dosing Recommendations

The starting dose of SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be based on the patient's current regimen.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be given twice daily with meals. The following doses are available:

50 mg sitagliptin/500 mg metformin hydrochloride
50 mg sitagliptin/1 g metformin hydrochloride

As initial therapy:

For patients with type 2 diabetes mellitus, whose hyperglycemia is inadequately controlled with diet and exercise alone, the recommended starting dose of SITAGLIPTIN + METFORMIN HCl (VELMETIA) is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients may be titrated up to 50 mg sitagliptin/1 g metformin hydrochloride twice daily.

For patients inadequately controlled on metformin monotherapy:

For patients not adequately controlled on metformin alone, the usual starting dose of SITAGLIPTIN + METFORMIN HCl (VELMETIA) should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

For patients inadequately controlled on sitagliptin monotherapy:

For patients inadequately controlled on sitagliptin alone, the usual starting dose of SITAGLIPTIN + METFORMIN HCl (VELMETIA) is 50 mg sitagliptin/500 mg metformin hydrochloride twice daily. Patients may be titrated up to 50 mg sitagliptin/1 g metformin hydrochloride twice daily. Patients taking sitagliptin monotherapy dose-adjusted for renal impairment should not be switched to SITAGLIPTIN + METFORMIN HCl (VELMETIA) (see **CONTRAINDICATIONS**).

For patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycemic agents: sitagliptin, metformin or a PPARγ agonist (i.e. thiazolidinediones):

The usual starting dose of SITAGLIPTIN + METFORMIN HCl (VELMETIA) should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered.

For patients switching from sitagliptin co-administered with metformin:

For patients switching from co-administration of sitagliptin and metformin, SITAGLIPTIN + METFORMIN HCl (VELMETIA) may be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycemic agents: sitagliptin, metformin or a sulfonylurea:

The usual starting dose of SITAGLIPTIN + METFORMIN HCl (VELMETIA) should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating a sulfonylurea may require lower sulfonylurea doses to reduce the risk of sulfonylurea-induced hypoglycemia (see **WARNINGS AND PRECAUTIONS**).

For patients inadequately controlled on dual combination therapy with any two of the following three antihyperglycemic agents: sitagliptin, metformin or insulin:

The usual starting dose of SITAGLIPTIN + METFORMIN HCl (VELMETIA) should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose). In determining the starting dose of the metformin component, the patient's level of glycemic control and current dose (if any) of metformin should be considered. Gradual dose escalation to reduce the gastrointestinal (GI) side effects associated with metformin should be considered. Patients currently on or initiating insulin therapy may require lower doses of insulin to reduce the risk of hypoglycemia (see **WARNINGS AND PRECAUTIONS**).

No studies have been performed specifically examining the safety and efficacy of SITAGLIPTIN + METFORMIN HCl (VELMETIA) in patients previously treated with other oral antihyperglycemic agents and switched to SITAGLIPTIN + METFORMIN HCl (VELMETIA). Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

<u>*Recommendations for use in renal impairment:*</u>

Assess renal function prior to initiation of SITAGLIPTIN + METFORMIN HCl (VELMETIA) and periodically thereafter.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is contraindicated in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m².

<u>SITAGLIPTIN + METFORMIN HCl (VELMETIA)</u>

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is not recommended in patients with an eGFR ≥ 30 mL/min/1.73 m² and < 45 mL/min/1.73 m² because these patients require a lower dosage of sitagliptin than what is available in the fixed combination SITAGLIPTIN + METFORMIN HCl (VELMETIA) product.

<u>*Discontinuation for iodinated contrast imaging procedures:*</u>

Discontinue SITAGLIPTIN + METFORMIN HCl (VELMETIA) at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m²; in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart SITAGLIPTIN + METFORMIN HCl (VELMETIA) if renal function is acceptable (see **WARNINGS AND PRECAUTIONS**).

MODE OF ADMINISTRATION

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is available for oral administration as tablets. It should generally be given twice daily with meals.

CONTRAINDICATIONS

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is contraindicated in patients with:

1. Severe renal impairment, (eGFR < 30 mL/min/1.73 m²) (see **WARNINGS AND PRECAUTIONS**, <u>Monitoring of renal function</u>).
2. Known hypersensitivity to sitagliptin phosphate, metformin hydrochloride or any other component of SITAGLIPTIN + METFORMIN HCl (VELMETIA) (see **WARNINGS AND PRECAUTIONS**, *Sitagliptin phosphate*, <u>Hypersensitivity Reactions</u> and **UNDESIRABLE EFFECTS**, *Postmarketing Experience*).
3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see **WARNINGS AND PRECAUTIONS**; *Metformin hydrochloride*).

WARNINGS AND PRECAUTIONS

SITAGLIPTIN + METFORMIN HCl (VELMETIA)

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

<u>Pancreatitis</u>: 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 + METFORMIN HCl (VELMETIA) and other potentially suspect medicinal products should be discontinued.

<u>Monitoring of renal function</u>: Metformin and sitagliptin are known to be substantially excreted by the kidney. The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. SITAGLIPTIN + METFORMIN HCl (VELMETIA) is contraindicated in severe renal impairment, patients with an eGFR < 30 mL/min/1.73 m² (see **RECOMMENDED DOSE, CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**, *Metformin hydrochloride*, <u>Lactic acidosis</u>).

Before initiation of therapy with SITAGLIPTIN + METFORMIN HCl (VELMETIA) and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and SITAGLIPTIN + METFORMIN HCl (VELMETIA) discontinued if evidence of renal impairment is present.

<u>Hypoglycemia in Combination with a Sulfonylurea or with Insulin:</u> As is typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin and metformin were 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**).

Sitagliptin phosphate

<u>Hypoglycemia in Combination with a Sulfonylurea or with Insulin</u>: In clinical trials of sitagliptin as monotherapy and as part of combination therapy with agents not known to cause hypoglycemia (i.e., metformin or a PPARγ agonist (thiazolidinedione), rates of hypoglycemia reported with sitagliptin were similar to rates in patients taking placebo. As typical with other antihyperglycemic agents, hypoglycemia has been observed when sitagliptin 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**).

<u>Hypersensitivity Reactions:</u> There have been postmarketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of SITAGLIPTIN + METFORMIN HCl (VELMETIA). 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, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue SITAGLIPTIN + METFORMIN HCl (VELMETIA), 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 + METFORMIN HCl (VELMETIA). If bullous pemphigoid is suspected, SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Metformin hydrochloride

<u>Lactic Acidosis:</u> Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with SITAGLIPTIN + METFORMIN HCl (VELMETIA); when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (> 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels > 5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications (see **RECOMMENDED DOSE**, *Recommendations for use in renal impairment*). Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function (see **USE IN THE ELDERLY**, *Metformin hydrochloride*). In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see **CONTRAINDICATIONS**).

<u>Hypoglycemia:</u> Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking β-adrenergic blocking drugs.

<u>Use of concomitant medications that may affect renal function or metformin disposition:</u> Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **INTERACTIONS WITH OTHER MEDICAMENTS**, *Metformin hydrochloride*), should be used with caution.

<u>Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials):</u> Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients with an eGFR ≥ 30 to < 60 mL/min/1.73 m², in patients with a history of hepatic impairment, alcoholism, or heart failure, or in patients who will be administered intra-arterial iodinated contrast, SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be acceptable (see **RECOMMENDED DOSE**).

<u>Hypoxic states:</u> Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on SITAGLIPTIN + METFORMIN HCl (VELMETIA) therapy, the drug should be promptly discontinued.

<u>Surgical procedures:</u> Use of SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as acceptable (see **RECOMMENDED DOSE**).

<u>Alcohol intake:</u> Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving SITAGLIPTIN + METFORMIN HCl (VELMETIA).

<u>Impaired hepatic function:</u> Since impaired hepatic function has been associated with some cases of lactic acidosis, SITAGLIPTIN + METFORMIN HCl (VELMETIA) should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

<u>Vitamin B_{12} levels:</u> In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on SITAGLIPTIN + METFORMIN HCl (VELMETIA) and any apparent abnormalities should be appropriately investigated and managed.

Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

<u>Change in clinical status of patients with previously controlled type 2 diabetes:</u> A patient with type 2 diabetes previously well controlled on SITAGLIPTIN + METFORMIN HCl (VELMETIA) who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, SITAGLIPTIN + METFORMIN HCl (VELMETIA) must be stopped immediately and other appropriate corrective measures initiated.

<u>Loss of control of blood glucose:</u> When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold SITAGLIPTIN + METFORMIN HCl (VELMETIA) and temporarily administer insulin. SITAGLIPTIN + METFORMIN HCl (VELMETIA) may be reinstituted after the acute episode is resolved.

INTERACTIONS WITH OTHER MEDICAMENTS

Sitagliptin and metformin

Co-administration of multiple doses of sitagliptin (50 mg b.i.d.) and metformin (1000 mg b.i.d.) did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with SITAGLIPTIN + METFORMIN HCl (VELMETIA) have not been performed; however, such studies have been conducted with the individual components of SITAGLIPTIN + METFORMIN HCl (VELMETIA), sitagliptin and metformin.

Sitagliptin phosphate

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.

Population pharmacokinetic analyses have been conducted in patients with type 2 diabetes. Concomitant medications did not have a clinically meaningful effect on sitagliptin pharmacokinetics. 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. 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 (JANUVIA®) 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 likely to be clinically meaningful.

Metformin hydrochloride

<u>Glyburide:</u> In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

<u>Furosemide:</u> A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

<u>Nifedipine:</u> A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

7007672003

Drugs that reduce metformin clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving SITAGLIPTIN + METFORMIN HCl (VELMETIA) the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

PREGNANCY and LACTATION

SITAGLIPTIN + METFORMIN HCl (VELMETIA)

There are no adequate and well-controlled studies in pregnant women with SITAGLIPTIN + METFORMIN HCl (VELMETIA) or its individual components; therefore, the safety of SITAGLIPTIN + METFORMIN HCl (VELMETIA) in pregnant women is not known. SITAGLIPTIN + METFORMIN HCl (VELMETIA), like other oral antihyperglycemic agents, is not recommended for use in pregnancy.

No animal studies have been conducted with the combined products in SITAGLIPTIN + METFORMIN HCl (VELMETIA) to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin phosphate

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 doses of 1000 mg/kg/day. However, animal reproduction studies are not always predictive of the human response.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing mothers

No studies in lactating animals have been conducted with the combined components of SITAGLIPTIN + METFORMIN HCl (VELMETIA). In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Therefore, SITAGLIPTIN + METFORMIN HCl (VELMETIA) should not be used by a woman who is nursing.

PEDIATRIC USE

The safety and efficacy of the addition of sitagliptin in pediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycemic control on metformin with or without insulin was assessed in two studies over 54 weeks. The addition of sitagliptin (administered as SITAGLIPTIN + METFORMIN HCl (VELMETIA)) was compared to the addition of placebo to metformin or metformin XR.

While superiority of HbA_1 reduction was demonstrated for SITAGLIPTIN + METFORMIN HCl (VELMETIA) over metformin at Week 20 in the pooled analysis of these two studies, results from the individual studies were inconsistent. Furthermore, efficacy for SITAGLIPTIN + METFORMIN HCl (VELMETIA) over metformin was not observed at Week 54. Therefore, these results do not support use of SITAGLIPTIN + METFORMIN HCl (VELMETIA) in pediatric subjects (10 to 17 years old) with type 2 diabetes.

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 + METFORMIN HCl (VELMETIA) have not been studied in pediatric patients under 10 years of age.

USE IN THE ELDERLY

SITAGLIPTIN + METFORMIN HCl (VELMETIA)

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function (See **WARNINGS AND PRECAUTIONS,** *Monitoring of Renal Function*).

Sitagliptin phosphate

In clinical studies, the safety and effectiveness of sitagliptin in the elderly (≥ 65 years) were comparable to those seen in younger patients (< 65 years).

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients.

UNDESIRABLE EFFECTS

In placebo-controlled clinical trials, in patients with type 2 diabetes mellitus, the combination of sitagliptin and metformin was generally well tolerated. The overall incidence of side effects reported in patients receiving the combination of sitagliptin and metformin was similar to that reported in patients receiving the combination of placebo and metformin.

Combination Therapy with Sitagliptin and Metformin

Initial Therapy

In a 24-week placebo-controlled factorial study of initial therapy with sitagliptin 50 mg twice daily in combination with metformin at 500 or 1000 mg twice daily, the drug-related adverse reactions reported in ≥ 1 % of patients receiving combination therapy (and greater than in patients receiving placebo) are shown in Table 1.

Table 1
Initial Therapy with Combination of Sitagliptin and Metformin: Drug-Related Adverse Reactions Reported in ≥ 1 % of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)[1]

	Number of Patients (%)			
	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 or 1000 mg b.i.d.	Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d.
	N = 176	N = 179	N = 364	N = 372
Diarrhea	2 (1.1)	0 (0.0)	12 (3.3)	13 (3.5)
Nausea	1 (0.6)	0 (0.0)	9 (2.5)	6 (1.6)
Dyspepsia	0 (0.0)	0 (0.0)	4 (1.1)	5 (1.3)
Flatulence	0 (0.0)	0 (0.0)	2 (0.5)	5 (1.3)
Vomiting	0 (0.0)	0 (0.0)	1 (0.3)	4 (1.1)
Headache	0 (0.0)	1 (0.6)	4 (1.1)	5 (1.3)
Hypoglycemia	0 (0.0)	1 (0.6)	2 (0.5)	4 (1.1)

[1] Intent-to-treat population.

[2] Data pooled for the patients given the lower and higher doses of metformin.

Add-on Combination Therapy to Metformin

In a 24-week placebo-controlled study of sitagliptin added to ongoing metformin therapy, 464 patients on metformin were treated with sitagliptin 100 mg once daily and 237 patients were given placebo with metformin. The only drug-related adverse reaction reported that occurred with an incidence of ≥ 1% and higher than placebo in patients receiving sitagliptin and metformin was nausea (100 mg sitagliptin and metformin, 1.1%, placebo and metformin, 0.4%)

Hypoglycemia and Gastrointestinal Adverse Experiences

In the placebo-controlled studies of combination therapy with sitagliptin and metformin, the incidence of hypoglycemia (regardless of investigator assessment of causality) reported in patients treated with the combination of sitagliptin and metformin was similar to that reported for patients treated with metformin and placebo. The incidences of pre-specified gastrointestinal adverse experiences in patients treated with the combination of sitagliptin and metformin were similar to those reported for patients treated with metformin alone. See Table 2.

Table 2
Hypoglycemia and Pre-specified Gastrointestinal Adverse Experiences (Regardless of Investigator Assessment of Causality) Reported in Patients Receiving Combination Therapy[1]

	Number of Patients (%)					
	Study of Sitagliptin and Metformin as Initial Therapy			Study of Sitagliptin as Add-on to Metformin		
	Placebo	Sitagliptin 100 mg q.d.	Metformin 500 or 1000 mg b.i.d. [2]	Sitagliptin 50 mg b.i.d. + Metformin 500 or 1000 mg b.i.d. [2]	Placebo and Metformin ≥ 1500 mg/day	Sitagliptin 100 mg q.d. and Metformin ≥ 1500 mg daily
	N = 176	N = 179	N = 364	N = 372	Nx 237	Nx 464
Hypoglycemia	1 (0.6)	1 (0.6)	3 (0.8)	6 (1.6)	5 (2.1)	6 (1.3)
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	6 (2.5)	11 (2.4)
Nausea	2 (1.1)	2 (1.1)	20 (5.5)	18 (4.8)	2 (0.8)	6 (1.3)
Vomiting	1 (0.6)	0 (0.0)	2 (0.5)	8 (2.1)	2 (0.8)	5 (1.1)
Abdominal Pain[3]	4 (2.3)	6 (3.4)	14 (3.8)	11 (3.0)	9 (3.8)	10 (2.2)

[1] In the study of initial therapy, Abdominal Discomfort was included with Abdominal Pain.

[2] Data pooled for the patients given the lower and higher doses of metformin.

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

Sitagliptin in Combination with Metformin and a Sulfonylurea

In a 24-week placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with glimepiride ≥ 4 mg daily and metformin ≥ 1500 mg daily, the drug-related adverse reactions reported in ≥ 1 % of patients treated with sitagliptin (N=116) and more commonly than in patients treated with placebo (N=113) were hypoglycemia (sitagliptin, 13.8%; placebo, 0.9%) and constipation (1.7%, 0.0%).

Sitagliptin in Combination with Metformin and a PPARγ Agonist

In a placebo-controlled study of sitagliptin 100 mg daily added to ongoing combination treatment with metformin and rosiglitazone, the drug-related adverse reactions reported through the primary time point at Week 18 in ≥ 1% of patients treated with sitagliptin (N=170) and more commonly than in patients treated with placebo (N=82) were: headache (sitagliptin, 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 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%).

Sitagliptin in Combination with Metformin and Insulin

In a 24-week placebo-controlled study of sitagliptin 100 mg added to ongoing combination treatment with metformin ≥ 1500 mg daily and stable-dose and insulin, the only drug-related adverse reaction reported in ≥ 1% of patients treated with sitagliptin (N=229) and more commonly than in patients treated with placebo (N=233) was hypoglycemia (sitagliptin, 10.9%; placebo, 5.2%). In another 24-week study of patients receiving sitagliptin as add-on therapy while undergoing insulin intensification (with or without metformin), the only drug-related adverse reaction reported in ≥ 1% in patients treated with sitagliptin and metformin and more commonly than in patients treated with placebo and metformin was vomiting (sitagliptin and metformin, 1.1%; placebo and metformin, 0.4%).

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*.

With the combination of sitagliptin and metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed.

Adverse Reactions with Sitagliptin

There were no drug-related adverse reactions reported that occurred with an incidence of ≥ 1% in patients receiving sitagliptin.

Adverse Reactions with Metformin

Adverse reactions reported (regardless of causality) in greater than 5% of patients treated with metformin and more commonly than in patients treated with placebo are diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Adverse reactions reported (regardless of causality) in greater than 5% of patients treated with metformin extended-release and more commonly than in patients treated with placebo are diarrhea and nausea/vomiting.

TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 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 and 1,034 treated with placebo). The overall incidence of serious adverse events in patients receiving sitagliptin 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-treated patients and 17.7% of the placebo-treated patients) and renal failure (1.4% of sitagliptin-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-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-treated patients and 0.7% in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3% in sitagliptin-treated patients and 0.2% in placebo-treated patients. The incidence of adjudication-confirmed malignancy events was 3.7% in sitagliptin-treated patients and 4.0% in placebo-treated patients.

Pediatric population

In a pooled analysis of two placebo-controlled clinical studies with SITAGLIPTIN + METFORMIN HCl (VELMETIA) in pediatric patients aged 10 to 17 years with type 2 diabetes, the drug-related adverse reactions reported through the 54-week treatment period in ≥1% of patients in the SITAGLIPTIN + METFORMIN HCl (VELMETIA) group (N=107) and more commonly than in patients in the Metformin/Metformin XR group (N=113) were diarrhea (SITAGLIPTIN + METFORMIN HCl (VELMETIA), 2.8%; Metformin/Metformin XR, 0.9%), nausea (2.8%, 0.9%), and hypoglycemia (6.5%, 3.5%).

The profile of side effects was comparable to that observed in adults. There were no clinically relevant differences between the SITAGLIPTIN + METFORMIN HCl (VELMETIA) and Metformin/Metformin XR 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 + METFORMIN HCl (VELMETIA) or sitagliptin, one of the components of SITAGLIPTIN + METFORMIN HCl (VELMETIA). These reactions have been reported when SITAGLIPTIN + METFORMIN HCl (VELMETIA) or sitagliptin have been used alone 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**, *Sitagliptin phosphate, 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.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

DATE OF REVISION OF PACKAGE INSERT

June 2022

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. You may also report an adverse event or product complaint directly to MSD Philippines through: dpoc_philippines@merck.com or +632-8784958. Seek medical attention immediately at the first sign of any adverse drug reaction.

Laboratory Test Findings

Sitagliptin phosphate

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin and metformin compared to patients treated with placebo and metformin. 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 a small 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.

Metformin hydrochloride

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to intrinsic factor deficiency in the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation (see **WARNINGS AND PRECAUTIONS**, *Metformin hydrochloride*).

OVERDOSAGE AND TREATMENT

Sitagliptin phosphate

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 **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 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.

Metformin hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **WARNINGS AND PRECAUTIONS**, *Metformin hydrochloride*). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

STORAGE CONDITION

Store at temperatures not exceeding 30°C (86°F).

DOSAGE FORMS AND PACKAGING AVAILABLE

Each SITAGLIPTIN + METFORMIN HCl (VELMETIA) 50 mg / 500 mg film-coated tablet contains 64.25 mg sitagliptin phosphate monohydrate equivalent to 50 mg sitagliptin as free base and 500 mg metformin hydrochloride, available in blister packs of 7's, box of 28's.

Each SITAGLIPTIN + METFORMIN HCl (VELMETIA) 50 mg / 1 g film-coated tablet contains 64.25 mg sitagliptin phosphate monohydrate equivalent to 50 mg sitagliptin as free base and 1 g metformin hydrochloride, available in blister packs of 7's, box of 28's.

WPR-MK0431A-T-062022
000025681-PH

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

SITAGLIPTIN METFORMIN HCl

VELMETIA®

Film-Coated Tablet
Antidiabetic

℞

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 + METFORMIN HCl (VELMETIA)?

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is a tablet that contains sitagliptin and metformin hydrochloride as active ingredients:

- SITAGLIPTIN + METFORMIN HCl (VELMETIA) 50 mg sitagliptin phosphate/500 mg metformin hydrochloride
- SITAGLIPTIN + METFORMIN HCl (VELMETIA) 50 mg sitagliptin phosphate/1 g metformin hydrochloride

SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be taken twice a day.

SITAGLIPTIN + METFORMIN HCl (VELMETIA) is a tablet that contains two prescription medicines, sitagliptin phosphate (JANUVIA®) and metformin, which lower blood sugar. Sitagliptin, a member of a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors), and metformin, a member of the biguanide class of medicines, work together to control blood sugar levels in patients with type 2 diabetes mellitus. Type 2 diabetes is also called non-insulin-dependent diabetes mellitus, or NIDDM.

- SITAGLIPTIN + METFORMIN HCl (VELMETIA) lowers blood sugar levels in patients with type 2 diabetes.
- SITAGLIPTIN + METFORMIN HCl (VELMETIA) helps to improve the levels of insulin after a meal.
- SITAGLIPTIN + METFORMIN HCl (VELMETIA) helps the body respond better to the insulin it makes naturally.
- SITAGLIPTIN + METFORMIN HCl (VELMETIA) decreases the amount of sugar made by the body.
- SITAGLIPTIN + METFORMIN HCl (VELMETIA) is unlikely to cause low blood sugar (hypoglycemia).

Why has my doctor prescribed SITAGLIPTIN + METFORMIN HCl (VELMETIA)?

Your doctor has prescribed SITAGLIPTIN + METFORMIN HCl (VELMETIA), along with diet and exercise, to help lower your blood sugar.

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 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 problems, kidney problems, 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 + METFORMIN HCl (VELMETIA)?

Who should not take SITAGLIPTIN + METFORMIN HCl (VELMETIA)?

You should not take SITAGLIPTIN + METFORMIN HCl (VELMETIA) if you:

- **have type 1 diabetes.**
- **have severe kidney problems.**
- **are allergic to sitagliptin (JANUVIA®), metformin hydrochloride, or any other components of SITAGLIPTIN + METFORMIN HCl (VELMETIA).** See **"What is SITAGLIPTIN + METFORMIN HCl (VELMETIA)?".**
- **have conditions called metabolic acidosis or diabetic ketoacidosis** (increased ketones in the blood or urine).
- **are going to get or receive an injection of dye or contrast agent for an x-ray procedure.** Talk to your doctor about when to stop SITAGLIPTIN + METFORMIN HCl (VELMETIA) and when to start again.
- plan to have surgery.
- are going to get or receive an injection of dye or contrast agent for an x-ray procedure.

What should I tell my doctor before and while taking SITAGLIPTIN + METFORMIN HCl (VELMETIA)?

You should tell your doctor if you:

- have severe kidney problems.
- have liver problems.
- have heart problems, including congestive heart failure.
- drink alcohol a lot (all the time or short-term "binge" drinking).
- are pregnant or planning to become pregnant.
- are breast-feeding.
- have or have had an allergic reaction to sitagliptin (JANUVIA), metformin, SITAGLIPTIN + METFORMIN HCl (VELMETIA).
- are taking any prescription medicines.
- are taking non-prescription medicines.
- are taking any herbal supplements.

While taking SITAGLIPTIN + METFORMIN HCl (VELMETIA)

Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving SITAGLIPTIN + METFORMIN HCl (VELMETIA). Pancreatitis can be a serious, potentially life-threatening medical condition. Stop taking SITAGLIPTIN + METFORMIN HCl (VELMETIA) 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 + METFORMIN HCl (VELMETIA). Tell your doctor if you develop blisters or the breakdown of your skin (erosion). Your doctor may tell you to stop taking SITAGLIPTIN + METFORMIN HCl (VELMETIA).

Use in children

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

Use in the elderly

SITAGLIPTIN + METFORMIN HCl (VELMETIA) should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

Use in pregnancy and breast-feeding

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

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

Can I take SITAGLIPTIN + METFORMIN HCl (VELMETIA) with other medicines?

SITAGLIPTIN + METFORMIN HCl (VELMETIA) may affect how well other drugs work and some drugs can affect how well SITAGLIPTIN + METFORMIN HCl (VELMETIA) works. Tell your doctor about all the medicines you take, including prescription, and non-prescription medicines and herbal supplements.

Can I drive or operate machinery while using SITAGLIPTIN + METFORMIN HCl (VELMETIA)?

There is no information to suggest that SITAGLIPTIN + METFORMIN HCl (VELMETIA) affect your ability to drive a car or operate machinery.

How should I take SITAGLIPTIN + METFORMIN HCl (VELMETIA)?

- Take SITAGLIPTIN + METFORMIN HCl (VELMETIA) exactly as your doctor has prescribed. Your doctor will tell you how many SITAGLIPTIN + METFORMIN HCl (VELMETIA) tablets to take and how often you should take them.
- Your doctor may need to increase your dose to control your blood sugar.
- Your doctor may prescribe SITAGLIPTIN + METFORMIN HCl (VELMETIA) along with a sulfonylurea, a glitazone or insulin (other medicines to lower blood sugar).
- Take SITAGLIPTIN + METFORMIN HCl (VELMETIA) twice daily with meals to lower your chance of an upset stomach.
- Continue to take SITAGLIPTIN + METFORMIN HCl (VELMETIA) as long as your doctor prescribes it so you can continue to help control your blood sugar.

You may need to stop SITAGLIPTIN + METFORMIN HCl (VELMETIA) for a short time. Call your doctor for instructions if you:

- have a condition that may be associated with dehydration (large loss of body fluids) such as being sick with severe vomiting, diarrhea or fever, or if you drink fluids a lot less than normal.

What should I do in case of an overdose?

If you take too much SITAGLIPTIN + METFORMIN HCl (VELMETIA), call your doctor or poison control center right away.

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 + METFORMIN HCl (VELMETIA).

What undesirable effects may SITAGLIPTIN + METFORMIN HCl (VELMETIA) have?

In rare cases, metformin, one of the medicines in SITAGLIPTIN + METFORMIN HCl (VELMETIA), can cause a serious side effect called lactic acidosis. Lactic acidosis is a medical emergency that can cause death and must be treated in the hospital. Lactic acidosis is caused by a build-up of lactic acid in your blood.

Stop taking SITAGLIPTIN + METFORMIN HCl (VELMETIA) if you get the following symptoms of lactic acidosis:

- You feel very weak and tired.
- You have unusual (not normal) muscle pain.
- You have trouble breathing.
- You have stomach pain with nausea and vomiting, or diarrhea.
- You feel cold, especially in your arms and legs.
- You feel dizzy or lightheaded.
- You have a slow or irregular heartbeat.
- Your medical condition suddenly changes.

You have a higher chance of getting lactic acidosis if you:

- have severe kidney problems.
- have liver problems.
- have congestive heart failure that requires treatment with medicines.
- drink a lot of alcohol (very often or short-term "binge" drinking).
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with activity or exercise and don't drink enough fluids.
- have certain x-ray tests with injectable dyes or contrast agents used.
- have surgery.
- have a heart attack, severe infection, or stroke.

Common side effects in patients taking metformin alone include diarrhea, nausea/vomiting, flatulence, weakness, indigestion, abdominal discomfort, and headache.

Common side effects in patients taking sitagliptin alone include stuffy or running nose and sore throat, upper respiratory tract infection, and headache.

Side effects seen in clinical trials using the combination of sitagliptin and metformin (the medicines in SITAGLIPTIN + METFORMIN HCl (VELMETIA)) were generally similar to metformin taken alone. Taking SITAGLIPTIN + METFORMIN HCl (VELMETIA) with meals can help reduce stomach side effects. However, if you have unusual and/or unexpected stomach problems, talk with your doctor. Stomach problems that start up again after treatment may be a sign of something more serious.

When SITAGLIPTIN + METFORMIN HCl (VELMETIA) is used with a sulfonylurea medicine or with insulin, low blood sugar (hypoglycemia), due to the sulfonylurea or insulin, can occur. Lower doses of the sulfonylurea medicine or insulin may be required. In addition, when SITAGLIPTIN + METFORMIN HCl (VELMETIA) is used with a sulfonylurea medicine, constipation may occur.

When SITAGLIPTIN + METFORMIN HCl (VELMETIA) was used in combination with rosiglitazone (a glitazone medicine), the following side effects were reported: headache, low blood sugar (hypoglycemia), diarrhea, upper respiratory infection, nausea, cough, fungal skin infection, swelling of the hands or legs, and vomiting.

Additional side effects have been reported in general use with SITAGLIPTIN + METFORMIN HCl (VELMETIA) or sitagliptin, one of the medicines in SITAGLIPTIN + METFORMIN HCl (VELMETIA). These side effects have been reported when SITAGLIPTIN + METFORMIN HCl (VELMETIA) or sitagliptin have been used by themselves 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 + METFORMIN HCl (VELMETIA) 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)
- Constipation
- Vomiting
- Joint pain
- Muscle aches
- Arm or leg pain
- Back pain
- Itching
- Blisters

Other side effects not listed above may also occur in some patients.

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 + METFORMIN HCl (VELMETIA) 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 + METFORMIN HCl (VELMETIA)?

Store at temperatures not exceeding 30°C (86°F).

Keep SITAGLIPTIN + METFORMIN HCl (VELMETIA) and all medicines safely away from children.

DOSAGE FORMS AND PACKAGING AVAILABLE

Each SITAGLIPTIN + METFORMIN HCl (VELMETIA) 50 mg / 500 mg Film-coated Tablet contains 64.25 mg sitagliptin phosphate monohydrate equivalent to 50 mg sitagliptin as free base and 500 mg metformin hydrochloride, available in blister packs of 7's, box of 28's.

Each SITAGLIPTIN + METFORMIN HCl (VELMETIA) 50 mg / 1 g Film-coated Tablet contains 64.25 mg sitagliptin phosphate monohydrate equivalent to 50 mg sitagliptin as free base and 1 g metformin hydrochloride, available blister packs of 7's, box of 28's.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

DATE OF REVISION OF PACKAGE INSERT

June 2022

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. You may also report an adverse event or product complaint directly to MSD Philippines through: dpoc_philippines@merck.com or +632-8784958. Seek medical attention immediately at the first sign of any adverse drug reaction.

Registration Numbers:

50 mg/500 mg Film-Coated Tablets:	Reg. No.: DRP-4010-01
50 mg/1 g Film-Coated Tablets:	Reg. No.: DRP-4012-01

Dates of First Authorization:

50 mg/500 mg Film-Coated Tablets:	December 10, 2012
50 mg/1g Film-Coated Tablets:	December 10, 2012

WPR-MK0431A-T-062022
000025681-PH

Manufactured by:
PATHEON PUERTO RICO, INC.
State Road 670 Km. 2.7
Manati, Puerto Rico, 00674, USA

Packed by:
HANGZHOU MSD PHARMACEUTICAL CO., LTD.
199, Wenhai North Road, HEDA, Hangzhou
Zhejiang Province, 310018, People's Republic of China

Imported by:
MERCK SHARP & DOHME (I.A.) LLC
26F AIA Tower, 8767 Paseo de Roxas
Makati City, Metro Manila, Philippines

Distributed by:
ESSEX PHARMACEUTICALS, INC.
26F AIA Tower, 8767 Paseo de Roxas
Makati City, Metro Manila, Philippines