Not to be sold by Retail without the prescription of a Registered Medical Practitioner

Rx

Sitagliptin Phosphate 50 mg & Metformin Hydrochloride 500 mg Tablets

OMNISITA-M

WARNING: LACTIC ACIDOSIS
See full prescribing information for complete boxed warning.
• Postmarketing cases of Metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio, and Metformin plasma levels generally >5 mcg/mL.
• Risk factors include renal impairment, concomitant use of certain drugs, age ≥65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage Metformin-associated lactic acidosis in these high risk groups are provided in the Full Prescribing Information.
• If lactic acidosis is suspected, discontinue Sitagliptin & Metformin Hydrochloride and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended.

1. Generic Name
Sitagliptin Phosphate 50 mg & Metformin Hydrochloride 500 mg Tablets

2. Qualitative and quantitative composition
Sitagliptin Phosphate 50 mg & Metformin Hydrochloride 500 mg Tablets
Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate IP 64.25mg
Equivalent to Sitagliptin 50 mg
Metformin Hydrochloride IP 500 mg
Colours: Ferric Oxide Red USP-NF, Ferric Oxide Black USP-NF & Titanium Dioxide IP

3. Dosage form and strength
Oral dosage form (Tablets)
Sitagliptin 50 mg & Metformin Hydrochloride 500 mg

4. Clinical particulars
4.1. Therapeutic indication
It is indicated as an adjunct to diet & exercise to improve glycemic control in patients with type-two diabetes mellitus.
FDC is indicated as triple combination therapy with a PPARγ agonist (i.e a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.
FDC is also indicated as add-on to insulin (i.e triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dosage of insulin and metformin alone do not provide adequate control.

4.2. Posology and method of administration
Recommended Dosing
Take Sitagliptin and Metformin Hydrochloride orally twice daily with meals.
• Individualize the dosage of both Sitagliptin and Metformin Hydrochloride on the basis of the patient's current regimen, effectiveness, and tolerability.
• The maximum recommended daily dose is 100 mg of Sitagliptin and 2000 mg of Metformin Hydrochloride.
• Do not split or divide Sitagliptin and Metformin Hydrochloride tablets.
• The recommended starting dose in patients not currently treated with Metformin is 50 mg Sitagliptin and 500 mg Metformin Hydrochloride twice daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with Metformin.
• The starting dose in patients already treated with Metformin should provide Sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and the dose of Metformin already being taken. For patients taking Metformin Hydrochloride 850 mg twice daily, the recommended starting dose of Sitagliptin and Metformin Hydrochloride is 50 mg Sitagliptin and 1000 mg Metformin Hydrochloride twice daily.

Recommendations for Use in Renal Impairment
• Assess renal function prior to initiation of Sitagliptin and Metformin Hydrochloride & periodically thereafter.
• Sitagliptin and Metformin Hydrochloride tablets are contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2.
• Sitagliptin and Metformin Hydrochloride is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m2 because these patients require a lower dosage of Sitagliptin than what is available in the fixed combination Sitagliptin and Metformin Hydrochloride product.

Discontinuation for Iodinated Contrast Imaging Procedures
Discontinue Sitagliptin and Metformin Hydrochloride at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 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 and Metformin Hydrochloride if renal function is stable.

4.3. Contraindications
Sitagliptin and Metformin Hydrochloride tablets is contraindicated in patients with:
• Severe renal impairment (eGFR<30ml/min./1.73m2).
• Acute or chronic metabolic acidosis, including Diabetes ketoacidosis.
• History of serious hypersensitivity rection to Sitagliptin and Metformin Hydrochloride tablets. or Sitagliptin, such as anaphylaxis or angioedema function in this population. Any dose adjustment should be based on a careful assessment of renal function.

4.4. Special warnings and precautions for use
Lactic acidosis
There have been postmarketing cases of Metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmia have occurred with severe acidosis. Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate/pyruvate ratio; Metformin plasma levels were generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If Metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Sitagliptin and Metformin Hydrochloride. In Sitagliptin and Metformin Hydrochloride treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated Metformin (Metformin Hydrochloride is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Sitagliptin and Metformin Hydrochloride and report these symptoms to their health care provider.

For each of the known and possible risk factors for Metformin-associated lactic acidosis, recommendations to reduce the risk of and manage Metformin-associated lactic acidosis are provided below:

Renal Impairment
The postmarketing Metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of Metformin accumulation and Metformin-associated lactic acidosis increases with the severity of renal impairment because Metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include:

• Before initiating Sitagliptin and Metformin Hydrochloride, obtain an estimated glomerular filtration rate (eGFR).
• Sitagliptin and Metformin Hydrochloride is contraindicated in patients with an eGFR below 30 mL/min/1.73 m2.
• Sitagliptin and Metformin Hydrochloride is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m2 because these patients require a lower dosage of Sitagliptin than what is available in the fixed combination Sitagliptin and Metformin Hydrochloride product.
• Obtain an eGFR at least annually in all patients taking Sitagliptin and Metformin Hydrochloride. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions
The concomitant use of Sitagliptin and Metformin Hydrochloride with specific drugs may increase the risk of Metformin associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase Metformin accumulation. Therefore, consider more frequent monitoring of patients.

Age 65 or Greater
The risk of Metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.

Radiological Studies with Contrast
Administration of intravascular iodinated contrast agents in Metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop Sitagliptin and Metformin Hydrochloride at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 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. Re-evaluate eGFR 48 hours after the imaging procedure, and restart Sitagliptin and Metformin Hydrochloride tablets if renal function is stable.

Surgery and Other Procedures
Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Sitagliptin and Metformin Hydrochloride should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States
Several of the postmarketing cases of Metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Sitagliptin and Metformin Hydrochloride tablets.
Excessive Alcohol Intake
Alcohol potentiates the effect of Metformin on lactate metabolism, and this may increase the risk of Metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Sitagliptin and Metformin Hydrochloride tablets.

Hepatic Impairment
Patients with hepatic impairment have developed with cases of Metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of Sitagliptin and Metformin Hydrochloride tablets in patients with clinical or laboratory evidence of hepatic disease.

Pancreatitis
There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking Sitagliptin and Metformin Hydrochloride tablets. After initiation of Sitagliptin and Metformin Hydrochloride tablets, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, Sitagliptin and Metformin Hydrochloride tablets should promptly be discontinued, and appropriate management should be initiated. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin and Metformin Hydrochloride tablets.

Heart Failure
An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease.

Consider the risks and benefits of Sitagliptin and Metformin Hydrochloride tablets prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment and observe these patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of Sitagliptin and Metformin Hydrochloride tablets.

Acute Renal Failure
There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with Sitagliptin and Metformin Hydrochloride tablets and at least annually thereafter, renal function should be assessed. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and Sitagliptin and Metformin Hydrochloride tablets discontinued if evidence of renal impairment is present. Sitagliptin and Metformin Hydrochloride is contraindicated in patients with severe renal impairment.

Vitamin B12 Deficiency
In controlled clinical trials of Metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of Metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 measurements at 2- to 3-year intervals in patients on Sitagliptin and Metformin Hydrochloride tablets and manage any abnormalities.

Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues
Sitagliptin and Metformin Hydrochloride tablets may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue (e.g., sulfonylurea). A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Sitagliptin and Metformin Hydrochloride tablets.

Hypersensitivity Reactions
There have been postmarketing reports of serious hypersensitivity reactions in patients treated with Sitagliptin, one of the components of Sitagliptin and Metformin Hydrochloride tablets. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with Sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue Sitagliptin and Metformin Hydrochloride tablets, assess for other potential causes for the event, and institute alternative treatment for diabetes.

Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Sitagliptin and Metformin Hydrochloride tablets.

Severe and Disabling Arthralgia
There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

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 and Metformin Hydrochloride tablets. If bullous pemphigoid is suspected, Sitagliptin and Metformin Hydrochloride tablets should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

4.5. Drug interactions
Table 1 presents clinically significant drug interactions with Sitagliptin and Metformin Hydrochloride tablets:

Table 1: Clinically Significant Drug Interactions with Sitagliptin and Metformin Hydrochloride tablets

Carbonic Anhydrase Inhibitors	
Clinical Impact:	Carbonic anhydrase inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Sitagliptin and Metformin Hydrochloride may increase the risk for lactic acidosis.
Intervention:	Consider more frequent monitoring of these patients
Examples:	Topiramate, zonisamide, acetazolamide or dichlorphenamide.
Drugs that Reduce Metformin Clearance	
Clinical Impact:	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) could increase systemic exposure to Metformin and may increase the risk for lactic acidosis.
Intervention:	Consider the benefits and risks of concomitant use with Sitagliptin and Metformin Hydrochloride tablets.
Examples:	Ranolazine, vandetanib, dolutegravir, and cimetidine.
Alcohol	
Clinical Impact:	Alcohol is known to potentiate the effect of Metformin on lactate metabolism.
Intervention:	Warn patients against alcohol intake while receiving Sitagliptin and Metformin Hydrochloride tablets.
Insulin Secretagogues or Insulin	
Clinical Impact:	Coadministration of Sitagliptin and Metformin Hydrochloride tablets with an insulin secretagogue (e.g., sulfonylurea) or insulin may increase the risk of hypoglycemia.
Intervention:	Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.
Drugs Affecting Glycemic Control	
Clinical Impact:	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.
Intervention:	When such drugs are administered to a patient receiving Sitagliptin and Metformin Hydrochloride tablets, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Sitagliptin and Metformin Hydrochloride tablets, observe the patient closely for hypoglycemia.
Examples:	Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Pregnancy
Risk Summary
The limited available data with Sitagliptin and Metformin Hydrochloride tablets in pregnant women are not sufficient to inform a drug associated risk for major birth defects and miscarriage. Published studies with Metformin use during pregnancy have not reported a clear association with Metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. No adverse developmental effects were observed when Sitagliptin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 30- times and 20-times, respectively, the 100 mg clinical dose, based on AUC. No adverse developmental effects were observed when Metformin was administered to pregnant Sprague Dawley rats and rabbits during organogenesis at doses up to 2- and 6-times, respectively, a 2000 mg clinical dose, based on body surface area.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a Hemoglobin A1c >7% and has been reported to be as high as 20-25% in women with a Hemoglobin A1c >10%.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data
Human Data
Published data from post-marketing studies do not report a clear association with Metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when Metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and inconsistent comparator groups.

Animal Data
Sitagliptin and Metformin Hydrochloride
No animal reproduction studies were conducted with the coadministration of Sitagliptin and Metformin.

Sitagliptin
In embryo-fetal development studies, Sitagliptin administered to pregnant rats and rabbits during organogenesis (gestation day 6 to 20) did not adversely affect developmental outcomes at oral doses up to 250 mg/kg (30-times the 100 mg clinical dose) and 125 mg/kg (20-times the 100 mg clinical dose), respectively, based on AUC. Higher doses in rats associated with maternal toxicity increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100-times the clinical dose, based on AUC. Placental transfer of Sitagliptin was observed in pregnant rats and rabbits. Sitagliptin administered to female rats from gestation day 6 to lactation day 21 caused no functional or behavioral toxicity in offspring of rats at doses up to 1000 mg/kg.

Metformin Hydrochloride
Metformin did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2- and 6-times a 2000 mg clinical dose based on body surface area (mg/m2) for rats and rabbits, respectively.

Lactation
Risk Summary
There is no information regarding the presence of Sitagliptin and Metformin Hydrochloride tablets in human milk, the effects on the breastfed infant, or the effects on milk production. Limited published studies report that Metformin is present in human milk. There are no reports of adverse effects on breastfed infants exposed to Metformin. There is no information on the effects of Metformin on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Sitagliptin and Metformin Hydrochloride tablets and any potential adverse effects on the breastfed infant from Sitagliptin and Metformin Hydrochloride tablets or from the underlying maternal condition.

Data
Sitagliptin
Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

Metformin Hydrochloride
Published clinical lactation studies report that Metformin is present in human milk, which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of Metformin during lactation because of small sample size and limited adverse event data collected in infants.

Females and Males of Reproductive Potential
Discuss the potential for unintended pregnancy with premenopausal women as therapy with Metformin may result in ovulation in some anovulatory women.

Pediatric Use
The safety and effectiveness of Sitagliptin and Metformin Hydrochloride tablets have not been established in pediatric patients.

Three 20-week double-blind, placebo-controlled studies each with 34-week extensions were conducted to evaluate the efficacy and safety of Sitagliptin in 410 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes, with or without insulin therapy (HbA1c 6.5-10% for patients not on insulin, HbA1c 7-10% for patients on insulin). At study entry, patients in study 1 were not treated with oral antihyperglycemic agents; patients in studies 2 and 3 were on maximally tolerated Metformin therapy. The primary efficacy endpoint was the change from baseline in HbA1c after 20 weeks of therapy. The pre-specified primary efficacy analyses included data from study 1 and pooled data from studies 2 and 3, regardless of glycemic rescue or treatment discontinuation.

In both efficacy analyses, the effect of treatment with Sitagliptin was not significantly different from placebo. In study 1, the mean baseline HbA1c was 7.5%, and 12% of patients were on insulin therapy. At week 20, the change from baseline in HbA1c in patients treated with Sitagliptin (N=95) was 0.06% compared to 0.23% in patients treated with placebo (N=95), a difference of -0.17% (95% CI: -0.62, 0.28). In studies 2 and 3, the mean baseline HbA1c was 8.0%, 15% of patients were on insulin and 72% were on Metformin Hydrochloride doses of greater than 1,500 mg daily. At week 20, the change from baseline in HbA1c in patients treated with Sitagliptin (N=107) was -0.23% compared to 0.09% in patients treated with placebo (N=113), a difference of -0.33% (95% CI: -0.70, 0.05).

Geriatric Use
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Renal function should be assessed more frequently in elderly patients.

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

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 young patients.

Renal Impairment
Sitagliptin and Metformin Hydrochloride is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m2 because these patients require a lower dosage of Sitagliptin than what is available in the fixed dose combination Sitagliptin and Metformin Hydrochloride tablets. Sitagliptin and Metformin Hydrochloride tablets is contraindicated in severe renal impairment, patients with an eGFR below 30 mL/min/1.73 m2.

Sitagliptin
Sitagliptin is excreted by the kidney, and Sitagliptin exposure is increased in patients with renal impairment.

Metformin Hydrochloride
Metformin is substantially excreted by the kidney, and the risk of Metformin accumulation and lactic acidosis increases with the degree of renal impairment.

Hepatic Impairment
Use of Metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Sitagliptin and Metformin Hydrochloride tablets are not recommended in patients with hepatic impairment.

4.7. Effects on ability to drive and use machines
Sitagliptin and Metformin Hydrochloride tablets has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported with Sitagliptin.

In addition, patients should be alerted to the risk of hypoglycaemia when Sitagliptin and Metformin Hydrochloride tablets are used in combination with a sulphonylurea or with insulin.

4.8. Undesirable effects
The following adverse reactions are also discussed elsewhere in the labeling:
• Lactic Acidosis
• Pancreatitis
• Heart Failure
• Acute Renal Failure
• Vitamin B12 Deficiency
• Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues
• Hypersensitivity Reactions
• Severe and Disabling Arthralgia
• Bullous Pemphigoid

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Sitagliptin and Metformin Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise.

Table 2 summarizes the most common (≥5% of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial study in which Sitagliptin and Metformin were coadministered to patients with type 2 diabetes inadequately controlled on diet and exercise.

Table 2: Sitagliptin and Metformin Coadministered to Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise:

Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Placebo)*

	Number of Patients (%)			
	Placebo	**Sitagliptin 100 mg once daily**	**Metformin Hydrochloride 500 mg/ Metformin Hydrochloride 1000 mg twice daily†**	**Sitagliptin 50 mg twice daily + Metformin Hydrochloride 500 mg/ Metformin Hydrochloride 1000 mg twice daily†**
	N = 176	**N = 179**	**N = 364†**	**N = 372†**
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)
Upper Respiratory Tract Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

* Intent-to-treat population.
† Data pooled for the patients given the lower and higher doses of Metformin.
Sitagliptin Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone
In a 24-week placebo-controlled trial of Sitagliptin 100 mg administered once daily added to a twice daily Metformin regimen, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (Sitagliptin and Metformin, 1.9%; placebo and Metformin, 2.5%).

Gastrointestinal Adverse Reactions
The incidences of pre-selected gastrointestinal adverse experiences in patients treated with Sitagliptin and Metformin were similar to those reported for patients treated with Metformin alone. See Table 3.

Table 3: Pre-selected Gastrointestinal Adverse Reactions (Regardless of Investigator Assessment of Causality) Reported in Patients with Type 2 Diabetes Receiving Sitagliptin and Metformin

	Number of Patients (%)					
	Study of Sitagliptin and Metformin in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Alone	
	Placebo	**Sitagliptin 100 mg once daily**	**Metformin Hydrochloride 500 mg/ Metformin Hydrochloride 1000 mg twice daily***	**Sitagliptin 50 mg twice daily + Metformin Hydrochloride 500 mg/ Metformin Hydrochloride 1000 mg twice daily***	**Placebo and Metformin Hydrochloride ≥ 1500 mg daily**	**Sitagliptin 100 mg once daily and Metformin Hydrochloride ≥ 1500 mg daily**
	N = 176	**N = 179**	**N = 364**	**N = 372**	**N = 237**	**N = 464**
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 (2.2)	2 (0.8)	5 (1.1)
Abdominal Pain†	4 (2.3)	6 (3.4)	14 (3.8)	11 (3.0)	9 (3.8)	10 (2.2)

* Data pooled for the patients given the lower and higher doses of Metformin.
† Abdominal discomfort was included in the analysis of abdominal pain in the study of initial therapy

Sitagliptin in Combination with Metformin and Glimepiride
In a 24-week placebo-controlled study of Sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on Metformin and glimepiride (Sitagliptin, N=116; placebo, N=113), the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with Sitagliptin and more commonly than in patients treated with placebo were: hypoglycemia (Table 3) and headache (6.9%, 2.7%).

Sitagliptin in Combination with Metformin and Rosiglitazone
In a placebo-controlled study of Sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on Metformin and rosiglitazone (Sitagliptin, N=181; placebo, N=97), the adverse reactions reported regardless of investigator assessment of causality through Week 18 in ≥5% of patients treated with Sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (Sitagliptin, 5.5%; placebo, 5.2%) and nasopharyngitis (6.1%, 4.1%). Through Week 54, the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with Sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (Sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%).

Sitagliptin in Combination with Metformin and Insulin
In a 24-week placebo-controlled study of Sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on Metformin and insulin (Sitagliptin, N=229; placebo, N=233), the only adverse reaction reported regardless of investigator assessment of causality in ≥5% of patients treated with Sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (Table 4).

Hypoglycemia
In the above studies (N=5), adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required although most (77%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When the combination of Sitagliptin and Metformin was coadministered with a sulfonylurea or with insulin, the percentage of patients reporting at least one adverse reaction of hypoglycemia was higher than that observed with placebo and Metformin coadministered with a sulfonylurea or with insulin (Table 4).

Table 4: Incidence and Rate of Hypoglycemia* (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Clinical Studies of Sitagliptin in Combination with Metformin Coadministered with Glimepiride or Insulin

Add-On to Glimepiride + Metformin (24 weeks)	**Sitagliptin 100 mg + Metformin + Glimepiride**	**Placebo + Metformin + Glimepiride**
	N = 116	N = 113
Overall (%)	19 (16.4)	1 (0.9)
Rate (episodes/patient-year)†	0.82	0.02
Severe (%)‡	0 (0.0)	0 (0.0)
Add-On to Insulin + Metformin (24 weeks)	**Sitagliptin 100 mg + Metformin + Insulin**	**Placebo + Metformin + Insulin**
	N = 229	N = 233
Overall (%)	35 (15.3)	19 (8.2)
Rate (episodes/patient-year)†	0.98	0.61
Severe (%)‡	1 (0.4)	1 (0.4)

* Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required: Intent-to-treat population.
† Based on total number of events (i.e., a single patient may have had multiple events).
‡ Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.
The overall incidence of reported adverse reactions of hypoglycemia in patients with type 2 diabetes inadequately controlled on diet and exercise was 0.6% in patients given placebo, 0.6% in patients given Sitagliptin alone, 0.8% in patients given Metformin alone, and 1.6% in patients given Sitagliptin in combination with Metformin. In patients with type 2 diabetes inadequately controlled on Metformin alone, the overall incidence of adverse reactions of hypoglycemia was 1.3% in patients given add-on Sitagliptin and 2.1% in patients given add-on placebo.

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

In an additional, 30-week placebo-controlled, study of patients with type 2 diabetes inadequately controlled with Metformin comparing the maintenance of Sitagliptin 100 mg versus withdrawal of Sitagliptin when initiating basal insulin therapy, the event rate and incidence of documented symptomatic hypoglycemia (blood glucose measurement ≤70 mg/dL) did not differ between the Sitagliptin and placebo groups.

Vital Signs and Electrocardiograms
With the combination of Sitagliptin and Metformin, no clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed.

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 acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for Sitagliptin and 4 patients with an event in 3942 patient-years for control).

Sitagliptin
The most common adverse experience in Sitagliptin monotherapy reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo was nasopharyngitis.

Metformin Hydrochloride
The most common (>5%) established adverse reactions due to initiation of Metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

Laboratory Tests
Sitagliptin
The incidence of laboratory adverse reactions was similar in patients treated with Sitagliptin and Metformin (7.6%) compared to patients treated with placebo and Metformin (8.7%). In most but not all 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 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 B12levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of Metformin or vitamin B12 supplementation.

Postmarketing Experience
Additional adverse reactions have been identified during post approval use of Sitagliptin and Metformin Hydrochloride tablets. 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; upper respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute renal failure (sometimes requiring dialysis); severe and disabling arthralgia; bullous pemphigoid; constipation; vomiting; headache; myalgia; pain in extremity; back pain; pruritus; mouth ulceration; stomatitis; cholestatic, hepatocellular, and mixed hepatocellular liver injury; rhabdomyolysis.

4.9. Overdose

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

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

Overdose of Metformin has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with Metformin has been established. Lactic acidosis has been reported in approximately 32% of Metformin overdose cases. 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.

5. Pharmacological properties
It combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes mellitus: Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and Metformin Hydrochloride, a member of the biguanide class.

5.1. Mechanism of action
Sitagliptin
Sitagliptin is a DPP-4 inhibitor, which is believed to exert its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones. Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

Metformin Hydrochloride
Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

5.2. Pharmacodynamic Properties
Sitagliptin
In patients with type 2 diabetes mellitus, administration of Sitagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased responsiveness of insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. In studies with healthy subjects, Sitagliptin did not lower blood glucose or cause hypoglycemia.

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

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 post dose was 8.0 msec. This increase is not considered to be clinically significant. At the 800-mg dose, peak Sitagliptin plasma concentrations were approximately 11 times higher than the peak concentrations following a 100-mg dose.

In patients with type 2 diabetes mellitus 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.

5.3 Pharmacokinetic Properties
Sitagliptin
The pharmacokinetics of Sitagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes mellitus. 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 in a dose-proportional manner and increased approximately 14% following 100 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for Sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of Sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption
Sitagliptin
After oral administration of a 100 mg dose to healthy subjects, Sitagliptin was rapidly absorbed with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours postdose. The absolute bioavailability of Sitagliptin is approximately 87%.

Effect of Food
Coadministration of a high-fat meal with Sitagliptin had no effect on the pharmacokinetics of Sitagliptin.

Metformin
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 1,500 mg, and 850 mg to 2,550 mg (approximately 1.3 times the maximum recommended daily dosage), indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Effect of Food
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 Hydrochloride with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

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

Metformin
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 <1mcg/ml.

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

Metformin
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.

Metabolism
Sitagliptin
Following a [14C]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
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.

Excretion
Sitagliptin
Following administration of an oral [14C]Sitagliptin dose to healthy subjects, approximately 100% of the administered radioactivity was eliminated in feces (13%) or urine (87%) within one week of dosing.

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 (P-gp), which may also be involved in mediating the renal elimination of Sitagliptin. However, cyclosporine, a P-gp inhibitor, did not reduce the renal clearance of Sitagliptin.

Metformin
Elimination of Metformin occurs primarily via renal excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of Metformin elimination.

Specific Populations
Patients with Renal Impairment
Studies characterizing the pharmacokinetics of Sitagliptin and Metformin after administration of Sitagliptin and Metformin Hydrochloride tablets in renally impaired patients have not been performed.

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

Metformin
In patients with decreased renal function, the plasma and blood half-life of Metformin is prolonged, and the renal clearance is decreased.

Patients with Hepatic Impairment
Studies characterizing the pharmacokinetics of Sitagliptin and Metformin after administration of Sitagliptin and Metformin Hydrochloride tablets in patients with hepatic impairment have not been performed.

Sitagliptin
In patients with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{max} of Sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100-mg dose of Sitagliptin. These differences are not considered to be clinically meaningful. There is no clinical experience in patients with severe hepatic impairment (Child Pugh score >9).

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

Effects of Age, Body Mass Index (BMI), Gender, and Race
Sitagliptin
Based on a population pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful effect on the pharmacokinetics of Sitagliptin. When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impact on the pharmacokinetics of Sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of Sitagliptin compared to younger subjects.

Metformin
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.

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

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

Drug Interaction Studies
Coadministration of multiple doses of Sitagliptin (50 mg) and Metformin Hydrochloride (1000 mg) given twice daily did not meaningfully alter the pharmacokinetics of either Sitagliptin or Metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with Sitagliptin and Metformin Hydrochloride tablets have not been performed; however, such studies have been conducted with the individual components of Sitagliptin and Metformin Hydrochloride tablets.

Sitagliptin
In Vitro Assessment of Drug Interactions
Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a P-gp substrate but does not inhibit P-gp mediated transport of digoxin. Based on these results, Sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of Sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

In Vivo Assessment of Drug Interactions
Effects of Sitagliptin on Other Drugs
In clinical studies, Sitagliptin did not meaningfully alter the pharmacokinetics of Metformin, glyburide, simvastatin, rosiglitazone, digoxin, warfarin, or an oral contraception (ethinyl estradiol and norethindrone) Table 5, providing in vivo evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, P-gp, and organic cationic transporter (OCT).

Table 5: Effect of Sitagliptin on Systemic Exposure of Coadministered Drugs

Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Sitagliptin***	**Geometric Mean Ratio (ratio with/without Sitagliptin) No Effect = 1.00**		
				AUC†	**C_{max}**
Digoxin	0.25 mg‡ once daily for 10 days	100 mg‡ once daily for 10 days	Digoxin	1.11§	1.18
Glyburide	1.25 mg	200 mg‡ once daily for 6 days	Glyburide	1.09	1.01
Simvastatin	20 mg	200 mg‡ once daily for 5 days	Simvastatin	0.85¶	0.80
			Simvastatin Acid	1.12¶	1.06
Rosiglitazone	4 mg	200 mg‡ once daily for 5 days	Rosiglitazone	0.98	0.99
Warfarin	30 mg single dose on day 5	200 mg‡ once daily for 11 days	S(-) Warfarin	0.95	0.89
			R(+) Warfarin	0.99	0.89
Ethinyl estradiol and norethindrone	21 days once daily of 35 µg ethinyl estradiol with norethindrone 0.5 mg x 7 days, 0.75 mg x 7 days, 1.0 mg x 7 days	200 mg‡ once daily for 21 days	Ethinyl estradiol	0.99	0.97
			Norethindrone	1.03	0.98
Metformin Hydrochloride	1000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Metformin	1.02#	0.97

* All doses administered as single dose unless otherwise specified.
† AUC is reported as AUC0-∞ unless otherwise specified.
‡ Multiple doses.
§ AUC 0-24hr.
¶ AUC 0-last.
# AUC 0-12hr.

Effects of Other Drugs on Sitagliptin
Clinical data described below suggest that Sitagliptin is not susceptible to clinically meaningful interactions by coadministered medications (Table 6).

Table 6: Effect of Coadministered Drugs on Systemic Exposure of Sitagliptin

Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Sitagliptin***	**Geometric Mean Ratio (Ratio with/ without Coadministered drug) No Effect = 1.00**		
				AUC†	**C_{max}**
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68
Metformin Hydrochloride	1000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Sitagliptin	1.02§	1.05

* All doses administered as single dose unless otherwise specified.
† AUC is reported as AUC0-∞ unless otherwise specified.
‡ Multiple dose
§ AUC0-12hr.

Metformin Hydrochloride

Table 7: Effect of Metformin Hydrochloride on Systemic Exposure of Coadministered Drugs

Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Metformin Hydrochloride***	**Geometric Mean Ratio (ratio with/without Metformin) No Effect = 1.00**		
				AUC†	C_{max}
Cimetidine	400 mg	850 mg	Cimetidine	0.95‡	1.01
Glyburide	5 mg	500 mg§	Glyburide	0.78¶	0.63¶
Furosemide	40 mg	850 mg	Furosemide	0.87¶	0.69¶
Nifedipine	10 mg	850 mg	Nifedipine	1.10‡	1.08
Propranolol	40 mg	850 mg	Propranolol	1.01‡	0.94
Ibuprofen	400 mg	850 mg	Ibuprofen	0.97#	1.01#

* All doses administered as single dose unless otherwise specified.
† AUC is reported as AUC0-∞ unless otherwise specified.
‡ AUC0-24hr.
§ Metformin Hydrochloride 500 mg.
¶ Ratio of arithmetic means, p value of difference <0.05
# Ratio of arithmetic means

Table 8: Effect of Coadministered Drugs on Systemic Exposure of Metformin Hydrochloride

Coadministered Drug	**Dose of Coadministered Drug***	**Dose of Metformin Hydrochloride***	**Geometric Mean Ratio (ratio with/without Coadministered drug) No Effect = 1.00**		
				AUC†	C_{max}
Glyburide	5 mg	500 mg‡	Metformin‡	0.98§	0.99§
Furosemide	40 mg	850 mg	Metformin	1.09§	1.22§
Nifedipine	10 mg	850 mg	Metformin	1.16	1.21
Propranolol	40 mg	850 mg	Metformin	0.90	0.94
Ibuprofen	400 mg	850 mg	Metformin	1.05§	1.07§
Drugs that are eliminated by renal tubular secretion may increase the accumulation of Metformin.					
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61
Carbonic anhydrase inhibitors may cause metabolic acidosis.					
Topiramate	100 mg¶	500 mg¶	Metformin	1.25¶	1.17

* All doses administered as single dose unless otherwise specified.
† AUC is reported as AUC0-∞ unless otherwise specified.
‡ Metformin Hydrochloride 500 mg.
§ Ratio of arithmetic means.
¶ Steady state 100 mg Topiramate every 12 hr + Metformin Hydrochloride 500 mg every 12 hr AUC = AUC0-12hr.

6. Nonclinical properties
6.1. Animal Toxicology or Pharmacology

No animal studies have been conducted with the combined products in Sitagliptin and Metformin Hydrochloride tablets to evaluate carcinogenesis, mutagenesis or impairment of fertility. The following data are based on the findings in studies with Sitagliptin and Metformin individually.

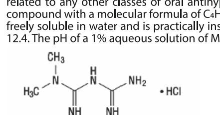
Sitagliptin
A two-year carcinogenicity study was conducted in male and female rats given oral doses of Sitagliptin of 50, 150, and 500 mg/kg/day. There was an increased incidence of combined liver adenoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results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

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

Metformin Hydrochloride
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with Metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with Metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

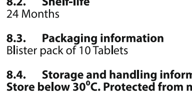
There was no evidence of a mutagenic potential of Metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative. Fertility of male or female rats was unaffected by Metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

7. Description
Sitagliptin
Sitagliptin is an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. Sitagliptin phosphate monohydrate is described chemically as 7-[(3R)-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 with an empirical formula of $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and a molecular weight of 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. Metformin Hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5 \cdot$Hydrochloride and a molecular weight of 165.63. Metformin Hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of Metformin Hydrochloride is 12.4. The pH of a 1% aqueous solution of Metformin Hydrochloride is 6.68. The structural formula is as shown:



8. Pharmaceutical particulars
8.1. Incompatibilities
Not Applicable

8.2. Shelf-life
24 Months

8.3. Packaging information
Blister pack of 10 Tablets

8.4. Storage and handling information
Store below 30°C. Protected from moisture.

9. Patient Counselling Information
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Lactic Acidosis
Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development. Advise patients to discontinue Sitagliptin and Metformin Hydrochloride tablets immediately and to promptly notify their healthcare provider if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptoms occur. Counsel patients against excessive alcohol intake and inform patients about the importance of regular testing of renal function while receiving Sitagliptin and Metformin Hydrochloride tablets. Instruct patients to inform their doctor that they are taking Sitagliptin and Metformin Hydrochloride tablets prior to any surgical or radiological procedure, as temporary discontinuation may be required.

Pancreatitis
Inform patients that acute pancreatitis has been reported during postmarketing use of Sitagliptin and Metformin Hydrochloride tablets. Inform patients that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to promptly discontinue Sitagliptin and Metformin Hydrochloride tablets and contact their physician if persistent severe abdominal pain occurs.

Heart Failure
Inform patients of the signs and symptoms of heart failure. Before initiating Sitagliptin and Metformin Hydrochloride tablets, ask patients about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Instruct patients to contact their health care provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet.

Vitamin B12 Deficiency
Inform patients about the importance of regular monitoring of hematological parameters while receiving Sitagliptin and Metformin Hydrochloride tablets.

Hypoglycemia
Inform patients that the incidence of hypoglycemia is increased when Sitagliptin and Metformin Hydrochloride tablets are added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Explain to patients receiving Sitagliptin and Metformin Hydrochloride tablets in combination with these medications the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development.

Hypersensitivity Reactions
Inform patients that allergic reactions have been reported during postmarketing use of Sitagliptin, one of the components of Sitagliptin and Metformin Hydrochloride tablets. If symptoms of allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking Sitagliptin and Metformin Hydrochloride tablets and seek medical advice promptly.

Severe and Disabling Arthralgia
Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs.

Bullous Pemphigoid
Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur.

Females of Reproductive Age
Inform females that treatment with Sitagliptin and Metformin Hydrochloride tablets may result in ovulation in some premenopausal anovulatory women which may lead to unintended pregnancy.

Administration Instructions
Inform patients that the tablets must never be split or divided before swallowing.

10. Details of Manufacturer
Manufactured in India by
Windlas Biotech Limited
(Plant-2), Khasra No. 141 to 143
& 145, Mohabewala Industrial Area,
Dehradun-248110, Uttarakhand.

11. Details of Permission or Licence Number with Date
Licence No.: 34/UA/2013; Dated: 03-02-2022

12. Date of Revision
April 2022

Marketed By:
Bioessentia LifeSciences
108, Sai Priya Grandeur Appt,
Doddathogur, ECity, Bengaluru,
Bangalore-Karnataka-560100

Front

Back

Leaflet
Unfolded Size: 180 x 460 mm
Black 100