

Summary of Product Characteristics

1. Name of the Medicinal Product

Tagipmet XR 50/1000 Tablets

2. Qualitative and Quantitative Composition

Each film coated tablets contains:

Sitagliptin (as phosphate Monohydrate) 50mg

Metformin HCl (Extended Release)1000mg

3. Pharmaceutical Form

oblong, plain, biconvex, light pink coloured, film coated tablet.

4. Clinical Particulars

4.1 Therapeutic indications

TAGIPMET XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin extended release is appropriate.

Important Limitations of Use:

TAGIPMET XR should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. TAGIPMET XR has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using TAGIPMET XR.

4.2 Posology and method of administration

Orally administered.

Recommended Dosing:

The dose of TAGIPMET XR 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 and 2000 mg metformin. Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

- In patients not currently treated with metformin, the recommended total daily starting dose of TAGIPMET XR is 100 mg sitagliptin and 1000 mg metformin hydrochloride (HCl) extended release. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose.

- In patients already treated with metformin, the recommended total daily starting dose of TAGIPMET XR is 100 mg sitagliptin and the previously prescribed dose of metformin.

- For patients taking metformin immediate-release 850 mg twice daily or 1000 mg twice daily, the recommended starting dose of TAGIPMET XR is two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets taken together once daily.

- Maintain the same total daily dose of sitagliptin and metformin when changing between TAGIPMET (sitagliptin and metformin HCl immediate-release) and TAGIPMET XR. Patients with inadequate glycemic control on this dose of metformin can be titrated gradually, to reduce gastrointestinal side effects associated with metformin, up to the maximum recommended daily dose.

TAGIPMET XR should be administered with food to reduce the gastrointestinal side effects associated with the metformin component.

TAGIPMET XR should be given once daily with a meal preferably in the evening. TAGIPMET XR should be swallowed whole. The tablets must not be split, crushed, or chewed before swallowing. The 100 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablet should be taken as a single tablet once daily. Patients using two TAGIPMET XR tablets (such as two 50 mg sitagliptin/500 mg metformin hydrochloride extended-release tablets or two 50 mg sitagliptin/1000 mg metformin hydrochloride extended-release tablets) should take the two tablets together once daily.

Patients treated with an insulin secretagogue or insulin:

Co-administration of TAGIPMET XR with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

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

4.3 Contraindications

TAGIPMET XR is contraindicated in patients with:

- Renal impairment (e.g., serum creatinine levels greater than or equal to 1.5 mg/dL for men, greater than or equal to 1.4 mg/dL for women or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- Hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis. Diabetic ketoacidosis should be treated with insulin.
- History of a serious hypersensitivity reaction to TAGIPMET XR or sitagliptin, such as anaphylaxis or angioedema.

4.4 Special warnings and special precautions for use:

Lactic Acidosis:

Metformin hydrochloride:

Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with TAGIPMET XR and 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 concentrations (>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 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 impairment, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. 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 TAGIPMET XR. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. TAGIPMET XR treatment should not be initiated in any patient unless measurement of creatinine clearance demonstrates that renal function is not reduced. In addition, TAGIPMET XR 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, TAGIPMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment. Patients should be cautioned against excessive alcohol intake when taking TAGIPMET XR, because alcohol potentiates the effects of metformin on lactate metabolism. In addition, TAGIPMET XR should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. Use of topiramate, a carbonic anhydrase inhibitor, in epilepsy and migraine prophylaxis may frequently cause dose-dependent metabolic acidosis (in controlled trials, 32% and 67% for adjunctive treatment in adults and pediatric patients, respectively, and 15 to 25% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 20 mEq/L; 3% and 11% for adjunctive treatment in adults and pediatric patients, respectively, and 1 to 7% for monotherapy of epilepsy, with decrease in serum bicarbonate to less than 17 mEq/L) and may exacerbate the risk of metformin-induced lactic acidosis. 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.

Patients should be educated to promptly report these symptoms to their physician should they occur. If present, TAGIPMET XR should be withdrawn until lactic acidosis is ruled out. Serum electrolytes, ketones, blood glucose, blood pH, lactate levels, and blood metformin levels may be useful. Once a patient is stabilized on any dose level of TAGIPMET XR, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to recur. 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 TAGIPMET XR 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 TAGIPMET XR, 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.

Pancreatitis:

There have been post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, in patients taking sitagliptin with or without metformin. After initiation of TAGIPMET XR, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, TAGIPMET XR 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 TAGIPMET XR.

Impaired Hepatic Function:

Since impaired hepatic function has been associated with some cases of lactic acidosis, TAGIPMET XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Assessment of Renal Function:

Metformin and sitagliptin are substantially excreted by the kidney.

Metformin hydrochloride:

The risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, TAGIPMET XR is contraindicated in patients with renal impairment. Before initiation of TAGIPMET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated (e.g., elderly), renal function should be assessed more frequently and TAGIPMET XR discontinued if evidence of renal impairment is present.

Sitagliptin:

There have been post-marketing reports of worsening renal function in patients taking sitagliptin with or without metformin, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with TAGIPMET XR and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, particularly in elderly patients, renal function should be assessed more frequently and TAGIPMET XR discontinued if evidence of renal impairment is present.

Vitamin B12 Levels:

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B12 levels, 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. Measurement of hematologic parameters on an annual basis is advised in patients on TAGIPMET XR and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B12 levels. In these patients, routine serum Vitamin B12 measurements at two- to three-year intervals may be useful.

Alcohol Intake:

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving TAGIPMET XR.

Surgical Procedures: Use of TAGIPMET XR 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 normal.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes:

A patient with type 2 diabetes previously well controlled on TAGIPMET XR 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, TAGIPMET XR must be stopped immediately and other appropriate corrective measures initiated.

Use with Medications Known to Cause Hypoglycemia:

Sitagliptin

When sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, patients also receiving an insulin secretagogue (e.g., sulfonylurea) or insulin may require a lower dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.

Metformin hydrochloride:

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.

Concomitant Medications Affecting Renal Function or Metformin Disposition

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, should be used with caution.

Radiologic Studies with Intravascular Iodinated Contrast Materials:

Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, TAGIPMET XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be normal.

Hypoxic States:

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 TAGIPMET XR therapy, the drug should be promptly discontinued.

Loss of Control of Blood Glucose:

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 TAGIPMET XR and temporarily administer insulin. TAGIPMET XR may be reinstated after the acute episode is resolved.

Hypersensitivity Reactions:

There have been post marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin, one of the components of TAGIPMET XR. 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 TAGIPMET XR, assess for other potential causes for the event, and institute alternative treatment for diabetes. Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with TAGIPMET XR.

Macrovascular Outcomes:

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with TAGIPMET XR or any other anti-diabetic drug.

4.5 Interactions with other medicinal products and other forms of interaction

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorophenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis. Use these drugs with caution in patients treated with TAGIPMET XR, as the risk of lactic acidosis may increase.

Cationic Drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of TAGIPMET XR and/or the interfering drug is recommended in patients who are taking

cationic medications that are excreted via the proximal renal tubular secretory system.

The Use of Metformin with Other Drugs

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 TAGIPMET XR the patient should be closely observed to maintain adequate glycemic control.

4.6 Pregnancy and lactation

Pregnancy:

Pregnancy Category B: TAGIPMET XR : There are no adequate and well-controlled studies in pregnant women with TAGIPMET XR or its individual components; therefore, the safety of TAGIPMET XR in pregnant women is not known. TAGIPMET XR should be used during pregnancy only if clearly needed. No animal studies have been conducted with the combined products in TAGIPMET XR to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

Sitagliptin

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

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

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

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

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended

human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively. However, because animal reproduction studies are not always predictive of human response, metformin hydrochloride should not be used during pregnancy unless clearly needed.

Nursing Mothers

No studies in lactating animals have been conducted with the combined components of TAGIPMET XR. 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 or metformin are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TAGIPMET XR is administered to a nursing woman.

Fertility

Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

4.7 Effects on ability to drive and use machines.

Tagipmet XR 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 Tagipmet XR is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable effects

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 Immediate-Release Co-administration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise.

Table 1 summarizes the most common ($\geq 5\%$ of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placebo-controlled factorial study in which sitagliptin and metformin immediate-release were co-administered to patients with type 2 diabetes inadequately controlled on diet and exercise.

Table 1: Sitagliptin and Metformin Immediate-Release Co-administered to Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise:

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

Number of Patients (%)				
Placebo	Sitagliptin 100 mg once daily	Metformin Immediate-Release 500 mg or 1000 mg twice daily †		Sitagliptin 50 mg twice daily + Metformin Immediate-Release 500 mg or 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 Immediate-Release Alone

In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice daily metformin immediate-release regimen, there were no adverse reactions reported regardless of investigator assessment of causality in $\geq 5\%$ 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 immediate-release, 1.9%; placebo and metformin immediate-release, 2.5%).

Gastrointestinal Adverse Reactions

The incidences of pre-selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin immediate-release were similar to those reported for patients treated with metformin immediate-release alone. See Table 2.

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

Number of Patients (%)					
Study of Sitagliptin and Metformin Immediate-Release in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlled on Metformin Immediate-Release Alone	
Placebo	Sitagliptin 100 mg once daily	Metformin Immediate-Release 500 mg or 1000 mg twice daily *	Sitagliptin 50 mg bid + Metformin Immediate-Release 500 mg or 1000	Placebo and Metformin Immediate-Release	Sitagliptin 100 mg once daily and Metformin Immediate-Release ≥ 1500 mg daily

			mg twice daily *	≥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 Immediate-Release 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 immediate-release 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 Immediate-Release 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 immediate-release 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 Immediate-Release 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 immediate-release and insulin (sitagliptin, N=229; placebo, N=233), the only adverse reaction reported regardless of investigator assessment of causality

in $\geq 5\%$ of patients treated with sitagliptin and more commonly than in patients treated with placebo was hypoglycemia (Table 3).

Hypoglycemia

In all (N=5) studies, 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 immediate-release was co-administered 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 immediate-release co-administered with a sulfonylurea or with insulin (Table 3).

Table 3: Incidence and Rate of Hypoglycemia* (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Clinical Studies of Sitagliptin in Combination with Metformin Immediate-Release Co-administered with Glimepiride or Insulin

Add-On to Glimepiride + Metformin Immediate-Release (24 weeks)	Sitagliptin 100 mg + Metformin Immediate-Release + Glimepiride	Placebo + Metformin Immediate-Release + 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 Immediate-Release (24 weeks)	Sitagliptin 100 mg + Metformin Immediate-Release + Insulin	Placebo + Metformin Immediate-Release + 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 immediate-release alone, and 1.6% in patients

given sitagliptin in combination with metformin immediate-release. In patients with type 2 diabetes inadequately controlled on metformin immediate-release 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 immediate-release 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.

Vital Signs and Electrocardiograms

With the combination of sitagliptin and metformin immediate-release, no clinically meaningful changes in vital signs or in electrocardiogram parameters (including the 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 $\geq 5\%$ of patients and more commonly than in patients given placebo was nasopharyngitis. Metformin Extended-Release In a 24-week clinical trial in which extended-release metformin or placebo was added to glyburide therapy, the most common ($>5\%$ and greater than placebo) adverse reactions in the combined treatment group were hypoglycemia (13.7% vs. 4.9%), diarrhea (12.5% vs. 5.6%), and nausea (6.7% vs. 4.2%).

Laboratory Tests

Sitagliptin:

The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin immediate-release (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 B12 levels, 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.

Post marketing Experience

Additional adverse reactions have been identified during post approval use of sitagliptin with or without metformin, and/or in combination with other antidiabetic medications. 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) constipation; vomiting; headache; arthralgia; myalgia; pain in extremity; back pain.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to the National Regulatory Agents.

4.9 Overdose

SITAGLIPTIN:

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

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

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. 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:

5.1 Pharmacodynamic properties

Mechanism of Action

TAGIPMET XR tablets combine two antidiabetic medications with complementary mechanisms of action to improve glycemic control in adults with type 2 diabetes: sitagliptin, a dipeptidyl peptidase-4 (DPP4) inhibitor, and metformin hydrochloride extended-release, a member of the biguanide class.

Sitagliptin

Sitagliptin is a DPP-4 inhibitor, which exerts 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 glucosedependent 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 a biguanide that improves glycemic control in patients with type 2 diabetes, 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. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or healthy subjects except in certain circumstances 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.

Pharmacodynamics:

Sitagliptin:

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

glucagon was associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Sitagliptin and Metformin hydrochloride Co-administration

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

Cardiac Electrophysiology

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

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

5.2 Pharmacokinetics and Metabolism

TAGIPMET XR The results of a study in healthy subjects demonstrated that the TAGIPMET XR (sitagliptin and metformin HCl extended-release) 50 mg/500 mg and 100 mg/1000 mg tablets are bioequivalent to coadministration of corresponding doses of sitagliptin and metformin hydrochloride extended-release.

Bioequivalence between two TAGIPMET XR 50 mg/500 mg tablets and one TAGIPMET XR 100 mg/1000 mg tablet was also demonstrated. After administration of two TAGIPMET XR 50 mg/1000 mg tablets once daily with the evening meal for 7 days in healthy adult subjects, steady-state for sitagliptin and metformin is reached by Day 4 and 5, respectively. The median T_{max} value for sitagliptin and metformin at steady state is approximately 3 and 8 hours post dose, respectively. The median T_{max} value for sitagliptin and metformin after administration of a single tablet of TAGIPMET is 3 and 3.5 hours post dose, respectively.

Absorption

TAGIPMET XR

After administration of TAGIPMET XR tablets with a high-fat breakfast, the AUC for sitagliptin was not altered. The mean C_{max} was decreased by 17%, although the median T_{max} was unchanged relative to the fasted state. After administration of TAGIPMET XR with a high-fat breakfast, the AUC for metformin increased 62%, the C_{max} for metformin decreased by 9%, and the median T_{max} for metformin occurred 2 hours later relative to the fasted state.

Sitagliptin

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

Distribution

Sitagliptin

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

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin hydrochloride tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins. 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.

Metabolism

Sitagliptin

Approximately 79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. Following a 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) or biliary excretion. Metabolism studies with extended-release metformin tablets have not been conducted.

Excretion

Sitagliptin

Following administration of an oral 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.

Specific Populations:

Renal Impairment

TAGIPMET XR

TAGIPMET XR should not be used in patients with renal impairment.

Sitagliptin

An approximately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment, 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 hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Impairment

Sitagliptin

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

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

Metformin hydrochloride

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

Gender

Sitagliptin

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

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.

Geriatric

Sitagliptin

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

Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects.

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. As is true for all patients, TAGIPMET XR treatment should not be initiated in geriatric patients unless measurement of creatinine clearance demonstrates that renal function is normal.

Pediatric:

No studies with TAGIPMET XR have been performed in pediatric patients.

Race

Sitagliptin:

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

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

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

Drug Interactions

Sitagliptin and Metformin hydrochloride Co-administration of multiple doses of sitagliptin (50 mg) and metformin (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 TAGIPMET XR have not been performed; however, such studies have been conducted with the individual components of TAGIPMET XR (sitagliptin and metformin hydrochloride extended-release).

Sitagliptin

In Vitro Assessment of Drug Interactions

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

5.3 Preclinical Safety Data

No animal studies have been conducted with Tagipmet.

In 16-week studies in which dogs were treated with either metformin alone or a combination of metformin and sitagliptin, no additional toxicity was observed from the combination. The NOEL in these studies was observed at exposures to sitagliptin of approximately 6 times the human exposure and to metformin of approximately 2.5 times the human exposure.

The following data are findings in studies performed with sitagliptin or metformin individually.

Sitagliptin

Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of

these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No treatment related effects on fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/post-natal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

Metformin

Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. Pharmaceutical Particulars

6.1 List of excipients

Hydroxypropylcellulose (Klucel EXF)
Microcrystalline Cellulose (Avicel PH 101)
Colloidal Silicon Dioxide (Aerosil 200)
Hydroxypropylmethylcellulose (HPMC K100M)
Magnesium Stearate
Hypromellose (Hydroxypropylmethylcellulose E5)

Polyethylene Glycol 6000 (Macrogol 6000)
Polysorbate 80 (Tween 80)
Talc
Titanium Dioxide
Iron Oxide Red
Simethicone Emulsion 30%

6.2 Incompatibilities

Not applicable

6.3 Special precautions for storage

Store at or below 30°C in a dry & dark place.

6.4 Presentation

14 tablets in blister pack, with printed aluminum foil 168 mm and Base or Cold Formable foil plain 170 mm and packed in bleached board unit carton UV coated.

6.5 Nature & Contents of Container

Blister Packing:

14 tablets in blister pack, with printed aluminum foil 168 mm and Base or Cold Formable foil plain 170 mm and packed in bleached board unit carton UV coated.

6.6 Instructions for use and handling

No special Instructions.

7. Marketing Authorization Holder

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8. Registration Numbers

CTD11195

9. Date of First Authorization:

Date of First Authorization: 08-06-2017

Date of next Renewal: 07-06-2022

10 **Date of Revision of Text**
Revised after every five years.