

**For the use of a Registered Medical Practitioner or Hospital or a Laboratory only**

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## **STALIX M**

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### **1. Generic Name**

Sitagliptin and metformin hydrochloride Tablets

### **2. Qualitative and quantitative Composition:**

#### **Stalix M 50+500mg**

Each Film-Coated Tablet Contains:

Sitagliptin phosphate monohydrate I.P. equivalent to Sitagliptin.... 50 mg

Metformin hydrochloride I.P. .... 500 mg

Excipients..... q.s.

Colours: Red oxide of iron, Yellow oxide of iron, Black oxide of iron and Titanium dioxide I.P.

Excipients are Microcrystalline cellulose (Avicel PH-102), Polyvinyl pyrrolidone, Sodium lauryl sulphate, Sorbitol, Crospovidone, Microcrystalline cellulose (Ceolus KG 1000), Sodium stearyl fumarate, Polyvinyl alcohol (Partially hydrolyzed), Macrogol/PEG, Talc, Titanium dioxide, Iron oxide red, Iron oxide yellow and Ferrosoferric oxide/Black iron oxide.

#### **Stalix M 50+850mg**

Each Film-Coated Tablet Contains:

Sitagliptin phosphate monohydrate I.P. equivalent to Sitagliptin.... 50 mg

Metformin hydrochloride I.P. .... 850 mg

Excipients..... q.s.

Colours: Red oxide of iron, Black oxide of iron and Titanium dioxide I.P.

#### **Stalix M 50+1000mg**

Each Film-Coated Tablet Contains:

Sitagliptin phosphate monohydrate I.P. equivalent to Sitagliptin.... 50 mg

Metformin hydrochloride I.P. .... 1000 mg

Excipients..... q.s.

Colours: Red oxide of iron, Black oxide of iron and Titanium dioxide I.P.

Excipients are Microcrystalline cellulose (Avicel PH-102), Polyvinyl pyrrolidone, Sodium lauryl sulphate, Sorbitol, Crospovidone, Microcrystalline cellulose (Ceolus KG 1000), Sodium stearyl fumarate, Polyvinyl alcohol (Partially hydrolyzed), Macrogol/PEG, Talc, Titanium dioxide, Iron oxide red and Ferrosoferric oxide/Black iron oxide.

### **3. Dosage form and strength**

**Dosage form:** Film-Coated Tablet

**Strength:** Sitagliptin Phosphate monohydrate 50 mg and metformin hydrochloride 500/ 850/ 1000mg

## 4. Clinical particulars

### 4.1 Therapeutic indication

A) FDC is indicated as triple combination therapy with a PPAR $\gamma$  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 PPAR $\gamma$  agonist.

B) FDC is also indicated as add-on to insulin (i.e triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when stable dosage of insulin and metformin alone do not provide adequate control.

### 4.2 Posology and method of administration

#### Posology

Dose: As directed by the Physician.

The dose of antihyperglycaemic therapy with Sitagliptin and metformin should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin.

#### *Adults with normal renal function (GFR $\geq$ 90 mL/min)*

##### For patients inadequately controlled on maximal tolerated dose of metformin monotherapy

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

##### For patients switching from co-administration of Sitagliptin and metformin

For patients switching from co-administration of sitagliptin and metformin, Sitagliptin and metformin should be initiated at the dose of Sitagliptin and metformin already being taken.

##### For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea

The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Sitagliptin and metformin is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia.

##### For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a PPAR $\gamma$ agonist

The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

##### For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin

The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Sitagliptin and metformin is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia.

For the different doses on metformin, Sitagliptin and metformin is available in strengths of 50 mg sitagliptin and 850 mg metformin hydrochloride or 1,000 mg metformin hydrochloride.

All patients should continue their recommended diet with an adequate distribution of carbohydrate intake during the day.

### **Special populations**

#### *Renal impairment*

No dose adjustment is needed for patients with mild renal impairment (glomerular filtration rate [GFR]  $\geq$  60 mL/min). A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

If no adequate strength of Sitagliptin and metformin is available, individual monocomponents should be used instead of the fixed-dose combination.

<b><u>GFR</u></b> <b><u>mL/min</u></b>	<b><u>Metformin</u></b>	<b><u>Sitagliptin</u></b>
60-89	Maximum daily dose is 3,000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100 mg.
45-59	Maximum daily dose is 2,000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100 mg.
30-44	Maximum daily dose is 1,000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50 mg.
< 30	Metformin is contraindicated.	Maximum daily dose is 25 mg.

#### *Hepatic impairment*

Sitagliptin and metformin must not be used in patients with hepatic impairment.

#### *Elderly*

As metformin and sitagliptin are excreted by the kidney, Sitagliptin and metformin should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly.

#### *Paediatric population*

Sitagliptin and metformin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy.

### **Method of administration**

Sitagliptin and metformin should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

### **4.3 Contraindications**

Sitagliptin and metformin is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- diabetic pre-coma;
- severe renal failure (GFR < 30 mL/min);
- acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock,
- intravascular administration of iodinated contrast agents;
- acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock,
- hepatic impairment;
- acute alcohol intoxication, alcoholism;
- breast-feeding.

### **4.4 Special warnings and precautions for use**

#### **General**

Sitagliptin and metformin should not be used in patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis.

#### **Acute pancreatitis**

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Sitagliptin and metformin and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Sitagliptin and metformin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

#### **Lactic acidosis**

Lactic acidosis, a rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe vomiting, diarrhoea, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes,

ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

#### Renal function

GFR should be assessed before treatment initiation and regularly thereafter. Sitagliptin and metformin is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued during conditions with the potential to alter renal function

#### Hypoglycaemia

Patients receiving Sitagliptin and metformin in combination with a sulphonylurea or with insulin may be at risk for hypoglycaemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary.

#### Hypersensitivity reactions

Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. 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, Sitagliptin and metformin should be discontinued, other potential causes of the event should be assessed, and alternative treatment for diabetes should be instituted.

#### Bullous pemphigoid

There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including sitagliptin. If bullous pemphigoid is suspected, Sitagliptin and metformin should be discontinued.

#### Surgery

Sitagliptin and metformin must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

#### Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Sitagliptin and metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

#### Change in clinical status of patients with previously controlled type 2 diabetes

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

#### **4.5 Drugs interactions**

Co-administration of multiple doses of sitagliptin (50 mg twice daily) and metformin (1,000 mg 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 have not been performed; however, such studies have been conducted with the individual active substances, sitagliptin and metformin.

##### Concomitant use not recommended

###### *Alcohol*

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

###### *Iodinated contrast agents*

Sitagliptin and metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

##### Combinations requiring precautions for use

Some medicinal products can adversely affect renal function, which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are co-administered.

Glucocorticoids (given by systemic and local routes) beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

##### Effects of other medicinal products on sitagliptin

*In vitro* and clinical data described below suggest that the risk for clinically meaningful interactions following co-administration of other medicinal products is low.

*In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin.

Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e., ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effects of potent CYP3A4 inhibitors in the setting of renal impairment have not been assessed in a clinical study.

*In vitro* transport studies showed that sitagliptin is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of sitagliptin was inhibited *in vitro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo*.

#### *Ciclosporin*

A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and  $C_{max}$  of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

#### Effects of sitagliptin on other medicinal products

##### *Digoxin*

Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma  $C_{max}$  on average by 18 %. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

*In vitro* data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p-glycoprotein *in vivo*.

## **4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)**

### Pregnancy

There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of sitagliptin.

A limited amount of data suggests the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development.

Sitagliptin and metformin should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment should be discontinued and the patient switched to insulin treatment as soon as possible.

### Breast-feeding

No studies in lactating animals have been conducted with the combined active substances of this medicinal product. In studies performed with the individual active substances, both Sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Sitagliptin and metformin must therefore not be used in women who are breast-feeding.

### 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**

Sitagliptin and metformin 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 is used in combination with a sulphonylurea or with insulin

## **4.8 Undesirable effects**

### Summary of the safety profile

There have been no therapeutic clinical trials conducted with Sitagliptin and metformin tablets however bioequivalence of Sitagliptin and metformin with co-administered Sitagliptin and metformin has been demonstrated. Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (13.8%) and insulin (10.9%).

### Sitagliptin and metformin

#### *Tabulated list of adverse reactions*

Adverse reactions are listed below as MedDRA preferred term by system organ class and absolute frequency (Table 1). Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

**The frequency of adverse reactions identified from placebo-controlled clinical studies of Sitagliptin and metformin alone, and post-marketing experience**

<b>Adverse reaction</b>	<b>Frequency of adverse reaction</b>
<b>Blood and lymphatic system disorders</b>	
thrombocytopenia	Rare
<b>Immune system disorders</b>	
hypersensitivity reactions including anaphylactic responses <sup>*,†</sup>	Frequency not known
<b>Metabolism and nutrition disorders</b>	



hypoglycaemia <sup>†</sup>	Common
<b>Nervous system disorders</b>	
somnolence	Uncommon
<b>Respiratory, thoracic and mediastinal disorders</b>	
interstitial lung disease*	Frequency not known
<b>Gastrointestinal disorders</b>	
diarrhoea	Uncommon
nausea	Common
flatulence	Common
constipation	Uncommon
upper abdominal pain	Uncommon
vomiting	Common
acute pancreatitis <sup>*,†,‡</sup>	Frequency not known
fatal and non-fatal haemorrhagic and necrotizing pancreatitis <sup>*,†</sup>	Frequency not known
<b>Skin and subcutaneous tissue disorders</b>	
pruritus <sup>*</sup>	Uncommon
angioedema <sup>*,†</sup>	Frequency not known
rash <sup>*,†</sup>	Frequency not known
urticaria <sup>*,†</sup>	Frequency not known
cutaneous vasculitis <sup>*,†</sup>	Frequency not known
exfoliative skin conditions including Stevens-Johnson syndrome <sup>*,†</sup>	Frequency not known
bullous pemphigoid <sup>*</sup>	Frequency not known

<b>Musculoskeletal and connective tissue disorders</b>	
arthralgia*	Frequency not known
myalgia*	Frequency not known
pain in extremity*	Frequency not known
back pain*	Frequency not known
arthropathy*	Frequency not known
<b>Renal and urinary disorders</b>	
impaired renal function*	Frequency not known
acute renal failure*	Frequency not known

Adverse reactions were identified through post-marketing surveillance.

Description of selected adverse reactions:

Some adverse reactions were observed more frequently in studies of combination use of Sitagliptin and metformin with other anti-diabetic medicinal products than in studies of Sitagliptin and metformin alone. These included hypoglycaemia (frequency very common with sulphonylurea or insulin), constipation (common with sulphonylurea), peripheral oedema (common with pioglitazone), and headache and dry mouth (uncommon with insulin).

*Sitagliptin*

In monotherapy studies of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions reported were headache, hypoglycaemia, constipation, and dizziness.

Among these patients, adverse events reported regardless of causal relationship to medicinal product occurring in at least 5 % included upper respiratory tract infection and nasopharyngitis. In addition, osteoarthritis and pain in extremity were reported with frequency uncommon (> 0.5 % higher among sitagliptin users than that in the control group).

*Metformin*

Gastrointestinal symptoms were reported very commonly in clinical studies and post-marketing use of metformin. Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases. Additional adverse reactions associated with metformin include metallic taste (common); lactic acidosis, liver function disorders, hepatitis, urticaria, erythema, and pruritus (very rare). Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g., megaloblastic anaemia).

Paediatric population

In reported clinical trials with Sitagliptin and metformin in paediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions was generally comparable to that

observed in adults. In paediatric patients on or not on background insulin, sitagliptin was associated with an increased risk of hypoglycaemia.

### *TECOS Cardiovascular Safety Study*

The reported Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was  $\geq 30$  and  $< 50$  mL/min/1.73 m<sup>2</sup>), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA<sub>1c</sub> and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

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

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: [http://www.torrentpharma.com/index.php/site/info/adverse\\_event\\_reporting](http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting).

By reporting side effects, you can help provide more information on the safety of this medicine.

## **4.9 Overdose**

During reported controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

A large overdose of metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

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

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

## **5 Pharmacological properties**

### **5.1 Mechanism of Action**

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

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.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- by delaying intestinal glucose absorption

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

## 5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD07

Sitagliptin and metformin combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

### Sitagliptin

#### *Clinical efficacy and safety*

Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment in adult patients with type 2 diabetes.

In clinical trials, sitagliptin as monotherapy improved glycaemic control with significant reductions in haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) and fasting and postprandial glucose. Reduction in fasting plasma glucose (FPG) was observed at 3 weeks, the first time point at which FPG was

measured. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy. Improvements in surrogate markers of beta cell function, including HOMA- $\beta$  (Homeostasis Model Assessment- $\beta$ ), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed.

#### Studies of sitagliptin in combination with metformin

In a 24-week, placebo-controlled clinical study to evaluate the efficacy and safety of the addition of sitagliptin 100 mg once daily to ongoing metformin, sitagliptin provided significant improvements in glycaemic parameters compared with placebo. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In this study there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

In a 24-week placebo-controlled factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1,000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline for patients on sitagliptin alone. The incidence of hypoglycaemia was similar across treatment groups.

### **Metformin**

#### *Clinical efficacy and safety*

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDLc and triglyceride levels.

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years),  $p=0.0023$ , and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years),  $p=0.0034$
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years,  $p=0.017$
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, ( $p=0.011$ ), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years ( $p=0.021$ )
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, ( $p=0.01$ ).

#### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of reported studies with Sitagliptin and metformin in all subsets of the paediatric population in type 2 diabetes mellitus.

The safety and efficacy of the addition of sitagliptin in paediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycaemic control on metformin with or without insulin was assessed in two studies over 54 weeks. The addition of sitagliptin (administered as sitagliptin +

metformin or sitagliptin + metformin extended release (XR)) was compared to the addition of placebo to metformin or metformin XR.

While superiority of HbA<sub>1c</sub> reduction was demonstrated for sitagliptin + metformin / sitagliptin + metformin XR over metformin at Week 20 in the pooled analysis of these two studies, results from the individual studies were inconsistent. Furthermore, greater efficacy for sitagliptin + metformin / sitagliptin + metformin XR compared to metformin was not observed at Week 54. Therefore, Sitagliptin and metformin should not be used in paediatric patients aged 10 to 17 years old because of insufficient efficacy.

### 5.3 Pharmacokinetic properties

#### **Sitagliptin and metformin**

A bioequivalence study in healthy subjects demonstrated that the Sitagliptin and metformin (sitagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of sitagliptin phosphate and metformin hydrochloride as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of Sitagliptin and metformin.

#### **Sitagliptin**

##### *Absorption*

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T<sub>max</sub>) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 Mm.hr, C<sub>max</sub> was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C<sub>max</sub> and C<sub>24hr</sub> (C<sub>max</sub> increased in a greater than dose-proportional manner and C<sub>24hr</sub> increased in a less than dose-proportional manner).

##### *Distribution*

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

##### *Biotransformation*

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

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

*In vitro* data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

##### *Elimination*

Following administration of an oral [<sup>14</sup>C]sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal t<sub>1/2</sub> following a 100-mg oral dose of sitagliptin was

approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The 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, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC<sub>50</sub>=160 µM) or p-glycoprotein (up to 250 µM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

### **Characteristics in patients**

The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

#### Renal impairment

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

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

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (GFR ≥ 30 to < 45 mL/min), and approximately 4-fold in patients with severe renal impairment (GFR < 30 mL/min), including patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis session starting 4 hours post-dose).

#### Hepatic impairment

No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

#### Elderly

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

#### Paediatric population

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. No studies with sitagliptin have been performed in paediatric patients < 10 years of age.

### ***Other patient characteristics***

No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics 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**

### ***Absorption***

After an oral dose of metformin,  $T_{max}$  is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 µg/mL. In a reported controlled clinical trials, maximum metformin plasma levels ( $C_{max}$ ) did not exceed 5 µg/mL, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

### ***Distribution***

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean  $V_d$  ranged between 63 – 276 L.

### ***Biotransformation***

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

### ***Elimination***

Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

## **6 Nonclinical properties**

### **6.1 Animal Toxicology or Pharmacology**

No reported animal studies have been conducted with Sitagliptin and metformin.

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).

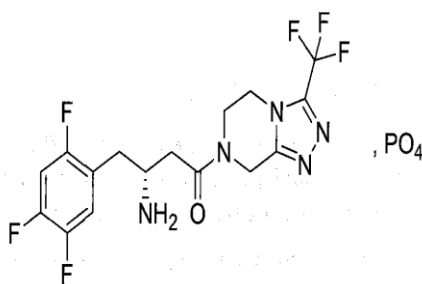
### **Metformin**

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.

## **7 Description**

### **Sitagliptin phosphate monohydrate:**

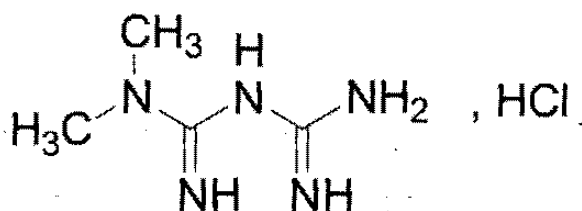
Sitagliptin Phosphate is (3R)-3-amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate monohydrate having molecular formula of C<sub>16</sub> H<sub>18</sub> F<sub>6</sub> N<sub>5</sub> O<sub>5</sub> P, H<sub>2</sub>O and molecular weight is 523.3 the chemical structure is:



Sitagliptin Phosphate monohydrate is a white or almost white powder. It is Soluble in water; very slightly soluble in ethanol; practically insoluble in heptane.

### Metformin Hydrochloride

Metformin Hydrochloride is 1, 1-dimethylbiguanide hydrochloride. The empirical formula of Metformin Hydrochloride is  $C_4H_{11}N_5, HCl$ . The molecular weight is 165.6. The chemical structure is:



**Metformin Hydrochloride** is a Metformin Hydrochloride is a white or almost white crystalline powder. It is Freely soluble in water; slightly soluble in ethanol, (95 per cent); practically insoluble in acetone, in chloroform, in dichloromethane and in ether.

**Stalix M 50+500mg** is Light pink, capsule shaped, film-coated tablets, plain on both sides.

**Excipients of Stalix M 50+500mg** are Microcrystalline cellulose (Avicel PH-102), Polyvinyl pyrrolidone, Sodium lauryl sulphate, Sorbitol, Crospovidone, Microcrystalline cellulose (Ceolus KG 1000), Sodium stearyl fumarate, Polyvinyl alcohol (Partially hydrolyzed), Macrogol/PEG, Talc, Titanium dioxide, Iron oxide red, Iron oxide yellow and Ferrosoferric oxide/Black iron oxide.

### Stalix M 50+850mg

Pink, capsule shaped, film-coated tablets, plain on both sides.

### Stalix M 50+1000mg

Red, capsule shaped, film-coated tablets, plain on both sides.

**Excipients of Stalix M 50+850mg and Stalix M 50+1000mg** are Microcrystalline cellulose (Avicel PH-102), Polyvinyl pyrrolidone, Sodium lauryl sulphate, Sorbitol, Crospovidone, Microcrystalline cellulose (Ceolus KG 1000), Sodium stearyl fumarate, Polyvinyl alcohol (Partially hydrolyzed), Macrogol/PEG, Talc, Titanium dioxide, Iron oxide red and Ferrosoferric oxide/Black iron oxide.

## 8 Pharmaceutical particulars

### 8.1 Incompatibilities

Not applicable

### 8.2 Shelf-life

Do not use later than date of expiry.

### 8.3 Packaging information

Stalix M Tablets is available blister pack of 15 tablets

### 8.4 Storage and handing instructions

- STORE AT A TEMPERATURE NOT EXCEEDING 30° C.

## 9 Patient Counselling Information

### Package leaflet: Information for the user

#### Stalix M

#### Sitagliptin and metformin hydrochloride Tablets

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

### What is in this leaflet

9.1 What Stalix M and what it is used for

9.2 What you need to know before you take Stalix M

9.3 How to take Stalix M

9.4 Possible side effects

9.5 How to store Stalix M

9.6 Contents of the pack and other information

### 9.1 What Stalix M is and what it is used for

Stalix M contains two different medicines called sitagliptin and metformin.

- Sitagliptin belongs to a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors)
- Metformin belongs to a class of medicines called biguanides.

They work together to control blood sugar levels in adult patients with a form of diabetes called 'type 2 diabetes mellitus'. This medicine helps to increase the levels of insulin produced after a meal and lowers the amount of sugar made by your body.

Along with diet and exercise, this medicine helps lower your blood sugar. This medicine can be used alone or with certain other medicines for diabetes (insulin, sulphonylureas, or glitazones).

### 9.2 What you need to know before you take Stalix M

#### **Do not take Stalix M :**

- if you are allergic to sitagliptin or metformin or any of the other ingredients of this medicine.
- if you have severely reduced kidney function

- if you have uncontrolled diabetes, with e.g. severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see “Risk of lactic acidosis” below) or ketoacidosis. Ketoacidosis is a condition in which substances called ‘ketone bodies’ accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.
- if you have a severe infection or are dehydrated
- if you are going to have an X-ray where you will be injected with a dye. You will need to stop taking Sitagliptin and metformin at the time of the X-ray and for 2 or more days after as directed by your doctor, depending on how your kidneys are working
- if you have recently had a heart attack or have severe circulatory problems, such as ‘shock’ or breathing difficulties
- if you have liver problems
- if you drink alcohol to excess (either every day or only from time to time)
- if you are breast-feeding

### **Do not take Stalix M**

if any of the above apply to you and talk with your doctor about other ways of managing your diabetes. If you are not sure, talk to your doctor, pharmacist or nurse before taking Sitagliptin and metformin.

### **Warnings and precautions**

Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving Stalix M.

If you encounter blistering of the skin it may be a sign for a condition called bullous pemphigoid. Your doctor may ask you to stop Stalix M.

### **Risk of lactic acidosis**

Stalix M may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).

If any of the above apply to you, talk to your doctor for further instructions.

**Stop taking Stalix M for a short time if you have a condition that may be associated with dehydration** (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

**Stop taking Stalix M and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis**, as this condition may lead to coma.

Symptoms of lactic acidosis include:

- vomiting
- stomachache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

Talk to your doctor or pharmacist before taking Stalix M :

- if you have or have had a disease of the pancreas (such as pancreatitis)
- if you have or have had gallstones, alcohol dependence or very high levels of triglycerides (a form of fat) in your blood. These medical conditions can increase your chance of getting pancreatitis.

if you have type 1 diabetes. This is sometimes called insulin-dependent diabetes

- if you have or have had an allergic reaction to sitagliptin, metformin, or Sitagliptin and metformin.
- if you are taking a sulphonylurea or insulin, diabetes medicines, together with Sitagliptin and metformin, as you may experience low blood sugar levels (hypoglycaemia). Your doctor may reduce the dose of your sulphonylurea or insulin
- If you need to have major surgery you must stop taking Sitagliptin and metformin during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Sitagliptin and metformin.
- If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking Sitagliptin and metformin.
- During treatment with Sitagliptin and metformin, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

### **Children and adolescents**

Children and adolescents below 18 years should not use this medicine. It is not effective in children and adolescents between the ages of 10 and 17 years. It is not known if this medicine is safe and effective when used in children younger than 10 years.

### **Other medicines and Stalix M**

If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example, in the context of an X-ray or scan, you must stop taking Sitagliptin and metformin before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Sitagliptin and metformin.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Sitagliptin and metformin. It is especially important to mention the following:

- medicines (taken by mouth, inhalation, or injection) used to treat diseases that involve inflammation, like asthma and arthritis (corticosteroids)
- medicines which increase urine production (diuretics)
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib)
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)
- specific medicines for the treatment of bronchial asthma ( $\beta$ -sympathomimetics)
- iodinated contrast agents or alcohol-containing medicines
- certain medicines used to treat stomach problems such as cimetidine
- ranolazine, a medicine used to treat angina
- dolutegravir, a medicine used to treat HIV infection
- vandetanib, a medicine used to treat a specific type of thyroid cancer (medullary thyroid cancer)

- digoxin (to treat irregular heartbeat and other heart problems). The level of digoxin in your blood may need to be checked if taking with Sitagliptin and metformin.

### **Stalix M with alcohol**

Avoid excessive alcohol intake while taking Sitagliptin and metformin since this may increase the risk of lactic acidosis.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not take this medicine during pregnancy or if you are breast-feeding.

### **Driving and using machines**

This medicine has no or negligible influence on the ability to drive and use machines. However, dizziness and drowsiness have been reported with sitagliptin, which may affect your ability to drive or use machines.

Taking this medicine in combination with medicines called sulphonylureas or with insulin can cause hypoglycaemia, which may affect your ability to drive and use machines or work without safe foothold.

## **9.3 How to take Stalix M**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- Take one tablet:
- twice daily by mouth
- with meals to lower your chance of an upset stomach.
- Your doctor may need to increase your dose to control your blood sugar.
- If you have reduced kidney function, your doctor may prescribe a lower dose.

You should continue the diet recommended by your doctor during treatment with this medicine and take care that your carbohydrate intake is equally distributed over the day.

This medicine alone is unlikely to cause abnormally low blood sugar (hypoglycaemia). When this medicine is used with a sulphonylurea medicine or with insulin, low blood sugar can occur and your doctor may reduce the dose of your sulphonylurea or insulin.

### **If you take more Stalix M than you should**

If you take more than the prescribed dosage of this medicine, contact your doctor immediately. Go to the hospital if you have symptoms of lactic acidosis such as feeling cold or uncomfortable, severe nausea or vomiting, stomachache, unexplained weight loss, muscular cramps, or rapid breathing.

### **If you forget to take Stalix M**

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

### **If you stop taking Stalix M**

Continue to take this medicine as long as your doctor prescribes it so you can continue to help control your blood sugar. You should not stop taking this medicine without talking to your doctor first. If you stop taking Stalix M, your blood sugar may rise again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

#### 9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

STOP taking Sitagliptin and metformin and contact a doctor immediately if you notice any of the following serious side effects:

- Severe and persistent pain in the abdomen (stomach area) which might reach through to your back with or without nausea and vomiting, as these could be signs of an inflamed pancreas (pancreatitis).

Stalix M may cause a very rare (may affect up to 1 in 10,000 people), but very serious side effect called lactic acidosis. If this happens, you must **stop taking Stalix M and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

If you have a serious allergic reaction (frequency not known), including rash, hives, blisters on the skin/peeling skin and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing, stop taking this medicine and call your doctor right away. Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes.

Some patients taking metformin have experienced the following side effects after starting sitagliptin:

**Common** (may affect up to 1 in 10 people): low blood sugar, nausea, flatulence, vomiting

**Uncommon** (may affect up to 1 in 100 people): stomachache, diarrhoea, constipation, drowsiness

Some patients have experienced diarrhoea, nausea, flatulence, constipation, stomachache or vomiting when starting the combination of Sitagliptin and metformin together (frequency is common).

Some patients have experienced the following side effects while taking this medicine with a sulphonylurea such as glimepiride:

**Very common** (may affect more than 1 in 10 people): low blood sugar

**Common:** constipation

Some patients have experienced the following side effects while taking this medicine in combination with pioglitazone:

**Common:** swelling of the hands or legs

Some patients have experienced the following side effects while taking this medicine in combination with insulin:

**Very common:** low blood sugar

**Uncommon:** dry mouth, headache

Some patients have experienced the following side effects during clinical studies while taking sitagliptin alone (one of the medicines in Sitagliptin and metformin) or during post-approval use of Sitagliptin and metformin or sitagliptin alone or with other diabetes medicines:

**Common:** low blood sugar, headache, upper respiratory infection, stuffy or runny nose and sore throat, osteoarthritis, arm or leg pain

**Uncommon:** dizziness, constipation, itching

**Rare:** reduced number of platelets

**Frequency not known:** kidney problems (sometimes requiring dialysis), vomiting, joint pain, muscle pain, back pain, interstitial lung disease, bullous pemphigoid (a type of skin blister)

Some patients have experienced the following side effects while taking metformin alone:

**Very common:** nausea, vomiting, diarrhoea, stomachache and loss of appetite. These symptoms may happen when you start taking metformin and usually go away

**Common:** a metallic taste

**Very rare:** decreased vitamin B12 levels, hepatitis (a problem with your liver), hives, redness of the skin (rash) or itching

## 9.5 How to store Stalix M

STORE AT A TEMPERATURE NOT EXCEEDING 30° C.

Keep all medicines out of reach of children.

## 9.6 Contents of the pack and other information

### What Stalix M contains

- The active substances are sitagliptin and metformin.
- **Excipients of Stalix M 50+500mg are** Microcrystalline cellulose (Avicel PH-102), Polyvinyl pyrrolidone, Sodium lauryl sulphate, Sorbitol, Crospovidone, Microcrystalline cellulose (Ceolus KG 1000), Sodium stearyl fumarate, Polyvinyl alcohol (Partially hydrolyzed), Macrogol/PEG, Talc, Titanium dioxide, Iron oxide red, Iron oxide yellow and Ferrosoferric oxide/Black iron oxide.
- **Excipients of Stalix M 50+850mg and Stalix M 50+1000mg are** Microcrystalline cellulose (Avicel PH-102), Polyvinyl pyrrolidone, Sodium lauryl sulphate, Sorbitol, Crospovidone, Microcrystalline cellulose (Ceolus KG 1000), Sodium stearyl fumarate, Polyvinyl alcohol (Partially hydrolyzed), Macrogol/PEG, Talc, Titanium dioxide, Iron oxide red and Ferrosoferric oxide/Black iron oxide.

### What Stalix M looks like and contents of the pack

Stalix M Tablets is available blister pack of 15 tablets.

## 10 Details of manufacturer

Torrent Pharmaceuticals Limited (Unit-II),

Plot No. 725 & 726, 32 No. Middle Camp,

NH-10, East District, Gangtok, -Sikkim-737 135.

## 11 Details of permission or licence number with date

M/785/2017 dated 02.03.2022

## 12. Date of revision

Not applicable

## MARKETED BY





TORRENT PHARMACEUTICALS LTD.

**IN/ STALIX M 50/500 and 850/ 1000 mg/MAR-22/01/PI**