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STALIX M

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**1. Generic Name**

Metformin and Sitagliptin Tablets B.P.

**2. Qualitative and quantitative Composition:**

**Stalix M 50+500 mg**

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, Opadry II Pink 85F540165.

**Stalix M 50+850 mg**

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.

Excipients are Microcrystalline cellulose (Avicel PH-102), Polyvinyl pyrrolidone, Sodium lauryl sulphate, Sorbitol, Crospovidone, Microcrystalline cellulose (Ceolus KG 1000), Sodium stearyl fumarate, Opadry II 85F540213 Pink.

**Stalix M 50+1000 mg**

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, Opadry II Brown 85F5651

**3. Dosage form and strength**

**Dosage form:** Film-Coated Tablet

**Strength:** 50+500, 50+850, 50+1000 Clinical particulars

#### 4.1. Therapeutic indication

It 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 is appropriate.

#### 4.2. Posology and method of administration

##### *Posology*

Dose: As directed by the Physician.

The dose of antihyperglycaemic therapy with Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P.

For patients switching from co-administration of Metformin and Sitagliptin Tablets B.P. , Metformin and Sitagliptin Tablets B.P. should be initiated at the dose of Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P. 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, Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P. 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*

Metformin and Sitagliptin Tablets B.P. must not be used in patients with hepatic impairment.

### *Elderly*

As metformin and sitagliptin are excreted by the kidney, Metformin and Sitagliptin Tablets B.P. 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*

Metformin and Sitagliptin Tablets B.P. should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy.

### ***Method of administration***

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

## **4.3. Contraindications**

Metformin and Sitagliptin Tablets B.P. 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**

Metformin and Sitagliptin Tablets B.P. 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, Metformin and Sitagliptin Tablets B.P. and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Metformin and Sitagliptin Tablets B.P. 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. Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P. 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, Metformin and Sitagliptin Tablets B.P. 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, Metformin and Sitagliptin Tablets B.P. should be discontinued.

### Surgery

Metformin and Sitagliptin Tablets B.P. 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. Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P. have not been performed; however, such studies have been conducted with the individual active substances, Metformin and Sitagliptin Tablets B.P.

#### 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*

Metformin and Sitagliptin Tablets B.P. 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<sub>max</sub> 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<sub>max</sub> 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.

Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P. 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. Metformin and Sitagliptin Tablets B.P. 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

Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P. 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 Metformin and Sitagliptin Tablets B.P. tablets however bioequivalence of Metformin and Sitagliptin Tablets B.P. with co-administered Metformin and Sitagliptin Tablets B.P. 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%).

##### Metformin and Sitagliptin Tablets B.P.

##### *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 Metformin and Sitagliptin Tablets B.P. 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 <sup>*</sup>	Frequency not known

<b>Adverse reaction</b>	<b>Frequency of adverse reaction</b>
<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 <sup>*</sup>	Frequency not known
myalgia <sup>*</sup>	Frequency not known
pain in extremity <sup>*</sup>	Frequency not known
back pain <sup>*</sup>	Frequency not known

<b>Adverse reaction</b>	<b>Frequency of adverse reaction</b>
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 Metformin and Sitagliptin Tablets B.P. with other anti-diabetic medicinal products than in studies of Metformin and Sitagliptin Tablets B.P. 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).

*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).

*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).

Paediatric population

In reported clinical trials with Metformin and Sitagliptin Tablets B.P. 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 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. Report suspected adverse reactions via any point of contact available at [www.torrentpharma.com](http://www.torrentpharma.com) or at email: [pv@torrentpharma.com](mailto:pv@torrentpharma.com) or call on 1800-120-3001.

## **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**

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).

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 insulintropic 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 Metformin and Sitagliptin Tablets B.P. had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

## 5.2. Pharmacodynamic properties

Metformin and Sitagliptin Tablets B.P. 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.

### 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 Metformin and Sitagliptin Tablets B.P. 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, Metformin and Sitagliptin Tablets B.P. should not be used in paediatric patients aged 10 to 17 years old because of insufficient efficacy.

### **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 Metformin and Sitagliptin Tablets B.P. 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.

### **5.3. Pharmacokinetic properties**

#### **Metformin and Sitagliptin Tablets B.P.**

A bioequivalence study in healthy subjects demonstrated that the Metformin and Sitagliptin Tablets B.P. (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 Metformin and Sitagliptin Tablets B.P..

## **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  $\mu\text{g/mL}$ . In a reported controlled clinical trials, maximum metformin plasma levels ( $C_{max}$ ) did not exceed 5  $\mu\text{g/mL}$ , 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  $> 400 \text{ mL/min}$ , 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.

## **Sitagliptin**

### *Absorption*

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median  $T_{max}$ ) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52  $\text{Mn}\cdot\text{hr}$ ,  $C_{max}$  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  $C_{max}$  and  $C_{24hr}$  ( $C_{max}$  increased in a greater than dose-proportional manner and  $C_{24hr}$  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  $t_{1/2}$  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  $\leq 9$ ). 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.

## **6. Nonclinical properties**

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

No reported animal studies have been conducted with Metformin and Sitagliptin Tablets B.P. .

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.

#### **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.

#### **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.

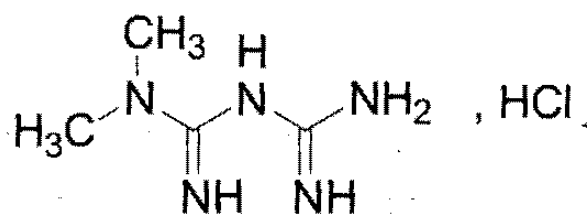
In a pre-/post-natal development study performed in rats sitagliptin showed no adverse effects.

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).

## 7. Description

### Metformin Hydrochloride

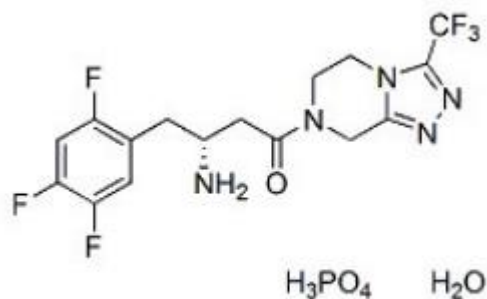
Metformin Hydrochloride is 1, 1-dimethylbiguanide hydrochloride. The empirical formula of Metformin Hydrochloride is  $C_4H_{11}N_5, HCl$ . The molecular weight is 165.6. The chemical structure is:



**Metformin Hydrochloride** is a 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.

### 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  $C_{16}H_{18}F_6N_5O_5P, H_2O$  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.

**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, Opadry II Pink 85F540165

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

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

**Excipients of Stalix M 50+850mg** are Microcrystalline cellulose (Avicel PH-102), Polyvinyl pyrrolidone, Sodium lauryl sulphate, Sorbitol, Crospovidone, Microcrystalline cellulose (Ceolus KG 1000), Sodium stearyl fumarate, Opadry II 85F540213 Pink.

#### **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, Opadry II Brown 85F5651

### **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 is available in 10 blister strips of 15 tablets each.

#### **8.4. Storage and handing instructions**

STORE AT A TEMPERATURE NOT EXCEEDING 25°C. Keep out of reach of children.

### **9. Patient Counselling Information**

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

**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 02.01.2023.

**12. Date of revision**

MAR 2026

**MARKETED BY**

**TORRENT**  
PHARMA

TORRENT PHARMACEUTICALS LTD.

**IN/STALIX M 50+500/850/1000 mg/MAR-2026/03/PI**