

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

---

**STALIX DM**

---

**1. Generic Name**

Dapagliflozin, Sitagliptin & Metformin Hydrochloride Extended Release Tablets

**2. Qualitative and quantitative Composition:**

**STALIX DM (10+100+1000 mg)**

Each film coated tablet contains:

Dapagliflozin Propanediol Monohydrate eq. to Dapagliflozin.....10 mg

Sitagliptin Phosphate Monohydrate I.P. eq. to Sitagliptin .....100 mg

Metformin Hydrochloride I.P. (as an extended release form).....1000 mg

Excipients .....q.s.

Colours: Indigo carmine Aluminum lake & Titanium dioxide I.P.

The excipients used are Colloidal Silicone Dioxide, Microcrystalline Cellulose, Mannitol, Indigo carmine Aluminum lake, Povidone K 30, Purified water, Croscarmellose Sodium, Magnesium Stearate, Hydroxypropylmethyl Cellulose, Isopropyl alcohol, Di calcium Phosphate Anhydrous, , Instacoat aqua II Blue.

**STALIX DM (10+100+500 mg)**

Each film coated tablet contains:

Dapagliflozin Propanediol Monohydrate eq .to Dapagliflozin..... 10 mg

Sitagliptin Phosphate Monohydrate I.P. eq. to Sitagliptin.....100 mg

Metformin Hydrochloride I.P.(as an extended release form ) .....500 mg

Excipients..... q. s.

Colours: Ferric oxide red USP-NF, Ferric oxide yellow USP-NF & Titanium dioxide I.P.

The excipients used are Colloidal Silicone Dioxide, Microcrystalline Cellulose, Mannitol, Iron oxide yellow, Povidone K 30, Purified water, Croscarmellose Sodium, Magnesium Stearate, Hydroxypropylmethyl Cellulose, Isopropyl alcohol, Di calcium Phosphate Anhydrous, Instacoat aqua II Peach.

**3. Dosage form and strength**

**Dosage form:** Film-coated Extended Release Tablet

**Strength:** Dapagliflozin 10 mg, Sitagliptin 100 mg and Metformin 1000 mg and Dapagliflozin 10 mg, Sitagliptin 100 mg and Metformin 500 mg

**4. 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.

## 4.2 **Posology and method of administration**

### **Posology**

Dose: As directed by the Physician.

### **Sitagliptin**

The dose is 100 mg sitagliptin once daily. When used in combination with metformin and/or a PPAR $\gamma$  agonist, the dose of metformin and/or PPAR $\gamma$  agonist should be maintained, and sitagliptin administered concomitantly.

When sitagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.

If a dose of sitagliptin is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

### **Special populations**

#### *Renal impairment*

When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked.

For patients with mild renal impairment (glomerular filtration rate [GFR]  $\geq 60$  to  $< 90$  mL/min), no dose adjustment is required.

For patients with moderate renal impairment (GFR  $\geq 45$  to  $< 60$  mL/min), no dosage adjustment is required.

For patients with moderate renal impairment (GFR  $\geq 30$  to  $< 45$  mL/min), the dose of Sitagliptin is 50 mg once daily.

For patients with severe renal impairment (GFR  $\geq 15$  to  $< 30$  mL/min) or with end-stage renal disease (ESRD) (GFR  $< 15$  mL/min), including those requiring haemodialysis or peritoneal dialysis, the dose of Sitagliptin is 25 mg once daily. Treatment may be administered without regard to the timing of dialysis.

Because there is a dosage adjustment based upon renal function, assessment of renal function is recommended prior to initiation of Sitagliptin and periodically thereafter.

#### *Hepatic impairment*

No dose adjustment is necessary for patients with mild to moderate hepatic impairment. Sitagliptin has not been studied in patients with severe hepatic impairment and care should be exercised.

However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

#### *Elderly*

No dose adjustment is necessary based on age.

#### *Paediatric population*

Sitagliptin should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Sitagliptin has not been studied in paediatric patients under 10 years of age.

### **Dapagliflozin**

#### *Type 2 diabetes mellitus*

The recommended dose is 10 mg dapagliflozin once daily.

When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

#### *Heart failure*

The recommended dose is 10 mg dapagliflozin once daily.

In the DAPA-HF study, dapagliflozin was administered in conjunction with other heart failure therapies.

#### *Chronic kidney disease*

The recommended dose is 10 mg dapagliflozin once daily.

In the DAPA-CKD study, dapagliflozin was administered in conjunction with other chronic kidney disease related therapies.

### **Special populations**

#### *Renal impairment*

No dose adjustment is required based on renal function.

It is not recommended to initiate treatment with dapagliflozin in patients with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m<sup>2</sup>.

In patients with type 2 diabetes mellitus, the glucose lowering efficacy of dapagliflozin is reduced when eGFR is < 45 mL/min/1.73m<sup>2</sup>, and is likely absent in patients with severe renal impairment. Therefore, if eGFR falls below 45 mL/min/1.73m<sup>2</sup>, additional glucose lowering treatment should be considered in patients with type 2 diabetes mellitus.

#### *Hepatic impairment*

No dose adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.

#### *Elderly (≥ 65 years)*

No dose adjustment is recommended based on age.

#### *Paediatric population*

No dose adjustment is required for the treatment of type 2 diabetes mellitus in children aged 10 years and above. No reported data are available for children below 10 years of age.

The safety and efficacy of dapagliflozin for the treatment of heart failure or for the treatment of chronic kidney disease in children < 18 years have not yet been established. No reported data are available.

### **Metformin**

Adults with normal renal function (GFR ≥ 90 mL/min)

#### **Monotherapy and combination with other oral antidiabetic agents:**

Metformin 500 mg film-coated tablets and Metformin 850 mg film-coated tablets

The usual starting dose is 500 mg or 850 mg metformin hydrochloride 2 or 3 times daily given during or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability.

The maximum recommended dose of metformin hydrochloride is 3 g daily, taken as 3 divided

doses.

#### Metformin 1000 mg film-coated tablets

For patients taking high doses of metformin hydrochloride (2 to 3 g daily), two Metformin 500 mg tablets may be replaced with Metformin 1000 mg film-coated tablets. The maximum recommended daily dose is 3 g metformin hydrochloride divided into 3 daily doses.

If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate metformin at the dose indicated above.

#### *Combination with insulin:*

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin hydrochloride is given at the usual starting dose of 500 mg or 850 mg 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

#### *Elderly:*

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

#### *Renal impairment*

GFR should be assessed before treatment with metformin-containing medicinal products begins and at least every year thereafter. In patients with increased risk of further impairment of renal function and in elderly, renal function should be assessed more often, e.g. every 3-6 months.

<b>GFRml/min</b>	<b>Total maximum daily dose (to be divided into 2-3 doses daily)</b>	<b>To consider</b>
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactate acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose
30-44	1000 mg	
< 30		Metformin is contraindicated.

#### *Children and adolescents:*

##### Paediatric population

##### Monotherapy and combination with insulin

- Metformin can be used in children from 10 years of age and adolescents.
- The usual starting dose is 500 mg or 850 mg metformin hydrochloride once daily, given during or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of metformin hydrochloride is 2 g daily, taken as 2 or 3 divided doses.

#### **Method of administration**

STALIX DM can be taken with or without food. Tablets are to be swallowed whole.

#### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

##### ***Metformin***

Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).

- Diabetic pre-coma.
- Sever renal failure (GFR < 30 ml/min).
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism.

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

##### **Sitagliptin**

###### **General**

Sitagliptin should not be used in patients with type 1 diabetes or 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 other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Sitagliptin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

###### **Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal products**

In clinical trials of Sitagliptin as monotherapy and as part of combination therapy with medicinal products not known to cause hypoglycaemia (i.e. metformin and/or a PPAR $\gamma$  agonist), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. Hypoglycaemia has been observed when sitagliptin was used in combination with insulin or a sulphonylurea. Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered.

###### **Renal impairment**

Sitagliptin is renally excreted. To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR < 45 mL/min, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis.

When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked.

###### **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 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 should be discontinued.

## ***Dapagliflozin***

### *Renal impairment*

There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m<sup>2</sup>, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m<sup>2</sup>. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m<sup>2</sup>.

The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with eGFR < 45 mL/min/1.73m<sup>2</sup> and is likely absent in patients with severe renal impairment.

In patients with moderate renal impairment (eGFR < 60 mL/min/1.73m<sup>2</sup>), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo.

### *Hepatic impairment*

There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.

### *Use in patients at risk for volume depletion and/or hypotension*

Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

### *Diabetic ketoacidosis*

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL).

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion,

unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.

Patients who may be at higher risk of DKA include patients with a low beta cell function reserve (e.g. type 2 diabetes patients with low C peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. Dapagliflozin should not be used for treatment of patients with type 1 diabetes.

#### *Necrotising fasciitis of the perineum (Fournier's gangrene)*

Postmarketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Dapagliflozin should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

#### *Urinary tract infections*

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or *urosepsis*.

#### *Elderly (≥ 65 years)*

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients.

#### *Cardiac failure*

Experience with dapagliflozin in NYHA class IV is limited.

## Chronic kidney disease

There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria.

Dapagliflozin has not been studied for the treatment of chronic kidney disease in patients with polycystic kidney disease, glomerulonephritis with flares (lupus nephritis or ANCA-associated vasculitis), ongoing or recent requirements of cytotoxic, immunosuppressive or other immunomodulating renal therapy, or in patients who received an organ transplant.

### *Lower limb amputations*

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

### *Urine laboratory assessments*

Due to its mechanism of action, patients taking Dapagliflozin will test positive for glucose in their urine.

## **Metformin**

### *Lactic acidosis:*

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), 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 diarrhoea or vomiting, 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 condition 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 muscle cramps, abdominal pain, 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. Metformin is contraindicated in patients with GFR <30 ml / min and should be temporarily discontinued in presence of conditions that alter renal function..

### *Cardiac function*

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with chronic stable heart failure, metformin may be used with regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated.

### *Administration of iodinated contrast media:*



Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy resulting in metformin accumulation and increased risk of lactate acidosis. Metformin should be discontinued before or at the time of imaging procedure and should not be reinstated until at least 48 hours after, provided that renal function has been evaluated and demonstrated to be stable.

*Surgery:*

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 reevaluated and found to be stable.

*Paediatric population:*

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated. No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially prepubescent children, is recommended.

Children aged between 10 and 12 years:

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

*Other precautions:*

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

## 4.5 **Drugs interactions**

### ***Sitagliptin***

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

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

In reported *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 effect of potent CYP3A4 inhibitors in the setting of renal impairment has not been assessed in a clinical study. In reported *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*.

- *Metformin:* Co-administration of multiple twice-daily doses of 1,000 mg metformin with 50

mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

- *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 Cmax 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 Cmax 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 reported *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*.

## ***Dapagliflozin***

### *Pharmacodynamic interactions*

#### *Diuretics*

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

#### *Insulin and insulin secretagogues*

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin in patients with type 2 diabetes mellitus.

### *Pharmacokinetic interactions*

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In reported *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes.

#### *Effect of other medicinal products on dapagliflozin*

In reported interaction studies conducted in healthy subjects, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure

(AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

#### *Effect of dapagliflozin on other medicinal products*

In reported interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

#### *Interference with 1,5-anhydroglucitol (1,5-AG) assay*

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use of alternative methods to monitor glycaemic control is advised.

#### *Paediatric population*

The reported interaction studies have only been performed in adults.

### **Metformin**

#### *Concomitant use not recommended:*

##### Alcohol:

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

##### Iodinated contrast agents

Metformin must be discontinued prior to, or at the time of the test and not be 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.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics):

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

#### Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

### Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

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

### Pregnancy

There are no reported adequate data from the use of sitagliptin in pregnant women. The reported studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, sitagliptin should not be used during pregnancy.

There are reported no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of dapagliflozin is not recommended during the second and third trimesters of pregnancy.

When pregnancy is detected, treatment with dapagliflozin should be discontinued.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the fetus.

### Breast-feeding

It is unknown whether sitagliptin is excreted in human breast milk. Animal studies have shown excretion of sitagliptin in breast milk. Sitagliptin should not be used during breast-feeding.

It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breastfeeding and the potential risk to adverse effects on the child.

### Fertility

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

The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

#### **4.7 Effects on ability to drive and use machines**

Sitagliptin 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.

In addition, patients should be alerted to the risk of hypoglycaemia when Sitagliptin is used in combination with a sulphonylurea or with insulin.

Dapagliflozin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

Metformin monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin or meglitinides).

#### **4.8 Undesirable effects**

##### Summary of the safety profile

Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (4.7 %-13.8 %) and insulin (9.6 %).

##### **Sitagliptin**

##### *Tabulated list of adverse reactions*

Adverse reactions are listed below (Table 1) by system organ class and frequency. 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 reported placebo-controlled clinical studies of Sitagliptin monotherapy 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	Frequency not known
<b>Metabolism and nutrition disorders</b>	
hypoglycaemia	Common
<b>Nervous system disorders</b>	
headache	Common
dizziness	Uncommon
<b>Respiratory, thoracic and mediastinal disorders</b>	
interstitial lung disease	Frequency not known
<b>Gastrointestinal disorders</b>	
constipation	Uncommon
vomiting	Frequency not known
acute pancreatitis	Frequency not known
fatal and non-fatal haemorrhagic and necrotizing pancreatitis	Frequency not known
<b>Skin and subcutaneous tissue disorders</b>	
pruritus	Uncommon
angioedema	Frequency not known
rash	Frequency not known
urticaria	Frequency not known
cutaneous vasculitis	Frequency not known
exfoliative skin conditions including Stevens-Johnson syndrome	Frequency not known
bullous pemphigoid	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:

In addition to the drug-related adverse experiences described above, adverse experiences reported regardless of causal relationship to medication and occurring in at least 5 % and more commonly in patients treated with sitagliptin included upper respiratory tract infection and nasopharyngitis. Additional adverse experiences reported regardless of causal relationship to medication that occurred more frequently in patients treated with sitagliptin (not reaching the 5 % level, but occurring with an incidence of > 0.5 % higher with sitagliptin than that in the control group) included osteoarthritis and pain in extremity.

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin with other anti-diabetic medicinal products than in studies of sitagliptin monotherapy. These included hypoglycaemia (frequency very common with the combination of sulphonylurea and metformin), influenza (common with insulin (with or without metformin)), nausea and vomiting (common with metformin), flatulence (common with metformin or pioglitazone), constipation (common with the combination of sulphonylurea and metformin), peripheral oedema (common with pioglitazone or the combination of pioglitazone and metformin), somnolence and diarrhoea (uncommon with metformin), and dry mouth (uncommon with insulin (with or without metformin)).

Paediatric population

In clinical trials with sitagliptin in paediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions was comparable to that observed in adults.

*TECOS Cardiovascular Safety Study*

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline 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 HbA1c 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 sulphonylurea 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 sulphonylurea 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.

## **Dapagliflozin**

### *Summary of the safety profile*

#### Type 2 diabetes mellitus

In reported clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.

The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.

In reported the dapagliflozin cardiovascular outcomes study in type 2 diabetes mellitus, 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections.

#### Heart failure

In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF study), 2,368 patients were treated with dapagliflozin 10 mg and 2,368 patients with placebo for a median exposure time of 18 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR  $\geq$  30 mL/min/1.73 m<sup>2</sup>.

The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

#### Chronic kidney disease

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR  $\geq$  25 to  $\leq$  75 mL/min/1.73 m<sup>2</sup>. Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m<sup>2</sup>.

The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin.

#### Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing surveillance. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: 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).

### **Table 1. Adverse reactions in placebo-controlled clinical studies and postmarketing experience**



<b>System organ class</b>	<b>Very common</b>	<b>Common*</b>	<b>Uncommon**</b>	<b>Rare</b>	<b>Very rare</b>
Infections and infestations		Vulvovaginitis, balanitis and related genital infections*, <sup>b,c</sup> Urinary tract infection*, <sup>b,d</sup>	Fungal infection**		Necrotising fasciitis of the perineum (Fournier's gangrene) <sup>b,i</sup>
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin) <sup>b</sup>		Volume depletion <sup>b,e</sup> Thirst**	Diabetic ketoacidosis (when used in type 2 diabetes mellitus) <sup>b,i,k</sup>	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation** Dry mouth**		
Skin and subcutaneous tissue disorders		Rash <sup>j</sup>			Angioedema
Musculoskeletal and connective tissue disorders		Back pain*			
Renal and urinary disorders		Dysuria Polyuria*, <sup>f</sup>	Nocturia**		

Reproductive system and breast disorders			Vulvovaginal pruritus** Pruritus genital**		
Investigations		Haematocrit increased <sup>g</sup> Creatinine renal clearance decreased during initial treatment <sup>b</sup> Dyslipidaemia <sup>h</sup>	Blood creatinine increased during initial treatment** <sup>b</sup> Blood urea increased** Weight decreased**		

<sup>a</sup>The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

<sup>b</sup>See corresponding subsection below for additional information.

<sup>c</sup>Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

<sup>d</sup>Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

<sup>e</sup>Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

<sup>f</sup>Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

<sup>g</sup>Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus -0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.

<sup>h</sup>Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%.

<sup>j</sup>Adverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4 %) and all control (1.4%), respectively.

<sup>k</sup>Reported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.

\*Reported in  $\geq 2\%$  of subjects and  $\geq 1\%$  more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

\*\*Reported by the investigator as possibly related, probably related or related to study treatment and reported in  $\geq 0.2\%$  of subjects and  $\geq 0.1\%$  more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

### Description of selected adverse reactions

#### Vulvovaginitis, balanitis and related genital infections

In the reported 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the reported DECLARE study, the numbers of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

In the reported DAPA-HF study, no patient reported serious adverse events of genital infections in the dapagliflozin group and one in the placebo group. There were 7 (0.3%) patients with adverse events leading to discontinuations due to genital infections in the dapagliflozin group and none in the placebo group.

In the reported DAPA-CKD study, there were 3 (0.1%) patients with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group. Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes.

#### Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin.

In the DECLARE study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

#### Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in the clinical studies in diabetes mellitus.

For studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar ( $< 5\%$ ) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia.

In an add-on to glimepiride study, at weeks 24 and 48, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0% and 7.9%, respectively) than in the placebo plus glimepiride group (2.1% and 2.1%, respectively).

In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects treated with dapagliflozin 10 mg plus insulin at weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at weeks 24 and 104. At weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin.

In an add-on to metformin and a sulphonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea.

In the DECLARE study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

In the reported DAPA-HF study, major events of hypoglycaemia were reported in 4 (0.2%) patients in both the dapagliflozin and placebo treatment groups and observed only in patients with type 2 diabetes mellitus.

In the reported DAPA-CKD study, major events of hypoglycaemia were reported in 14 (0.7%) patients in the dapagliflozin group and 28 (1.3%) patients in the placebo group and observed only in patients with type 2 diabetes mellitus.

#### *Volume depletion*

In the reported 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo.

In the reported DECLARE study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and angiotensin converting enzyme inhibitors (ACE-I)/angiotensin II type 1 receptor blockers (ARB) use. In patients with eGFR < 60 mL/min/1.73 m<sup>2</sup> at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

In the reported DAPA-HF study, the numbers of patients with events suggestive of volume depletion were 170 (7.2%) in the dapagliflozin group and 153 (6.5%) in the placebo group. There were fewer patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group (23 [1.0%]) compared with the placebo group (38 [1.6%]). Results were similar irrespective of presence of diabetes at baseline and baseline eGFR.

In the reported DAPA-CKD study, the numbers of patients with events suggestive of volume depletion were 120 (5.6%) in the dapagliflozin group and 84 (3.9%) in the placebo group. There were 16 (0.7%) patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group and 15 (0.7%) patients in the placebo group.

#### *Diabetic ketoacidosis in type 2 diabetes mellitus*

In the reported DECLARE study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in

the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population.

In the reported DAPA-HF study, events of DKA were reported in 3 patients with type 2 diabetes mellitus in the dapagliflozin group and none in the placebo group.

In the reported DAPA-CKD study, events of DKA were not reported in any patient in the dapagliflozin group and in 2 patients with type 2 diabetes mellitus in the placebo group.

#### *Urinary tract infections*

In the reported 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

In the reported DECLARE study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

In the reported DAPA-HF study, the numbers of patients with serious adverse events of urinary tract infections were 14 (0.6%) in the dapagliflozin group and 17 (0.7%) in the placebo group. There were 5 (0.2%) patients with adverse events leading to discontinuations due to urinary tract infections in each of the dapagliflozin and placebo groups.

In the reported DAPA-CKD study, the numbers of patients with serious adverse events of urinary tract infections were 29 (1.3%) in the dapagliflozin group and 18 (0.8%) in the placebo group. There were 8 (0.4%) patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 3 (0.1%) in the placebo group. The numbers of patients without diabetes reporting serious adverse events of urinary tract infections or adverse events leading to discontinuation due to urinary tract infections were similar between treatment groups (6 [0.9%] versus 4 [0.6%] for serious adverse events, and 1 [0.1%] versus 0 for adverse events leading to discontinuation, in the dapagliflozin and placebo groups, respectively).

#### *Increased creatinine*

Adverse reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). In the 13-study safety pool, this grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR  $\geq$  60 mL/min/1.73 m<sup>2</sup>) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR  $\geq$  30 and  $<$  60 mL/min/1.73 m<sup>2</sup> (18.5% dapagliflozin 10 mg versus 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of  $\leq$  0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In the reported DECLARE study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m<sup>2</sup>), eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

In the reported DAPA-HF study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial decrease in mean eGFR was -4.3 mL/min/1.73 m<sup>2</sup> in the dapagliflozin

group and -1.1 mL/min/1.73 m<sup>2</sup> in the placebo group. At 20 months, change from baseline in eGFR was similar between the treatment groups: -5.3 mL/min/1.73 m<sup>2</sup> for dapagliflozin and -4.5 mL/min/1.73 m<sup>2</sup> for placebo.

In the reported DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was -4.0 mL/min/1.73 m<sup>2</sup> in the dapagliflozin group and -0.8 mL/min/1.73 m<sup>2</sup> in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 m<sup>2</sup> in the dapagliflozin group and -8.6 mL/min/1.73 m<sup>2</sup> in the placebo group.

#### *Paediatric population*

The dapagliflozin safety profile observed in a clinical study in children aged 10 years and above with type 2 diabetes mellitus was similar to that observed in the studies in adults.

#### **Metformin**

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows

very common:  $\geq 1/10$ ; common  $\geq 1/100$ ,  $< 1/10$ ; uncommon  $\geq 1/1,000$ ,  $< 1/100$ ; rare  $\geq 1/10,000$ ,  $< 1/1,000$ ; very rare  $< 1/10,000$ .

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

#### *Metabolism and nutrition disorders:*

Very rare:

Lactic acidosis.

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

#### *Nervous system disorders:*

Common: Taste disturbance

#### *Gastrointestinal disorders:*

Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

#### *Hepatobiliary disorders:*

Very rare: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

#### *Skin and subcutaneous tissue disorders:*

Very rare: Skin reactions such as erythema, pruritus, urticaria

#### *Paediatric population*

In published and post marketing data and in controlled clinical studies in a limited paediatric

population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

### **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**

### **Sitagliptin**

During 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.

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

Sitagliptin is modestly dialysable. 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.

### **Dapagliflozin**

Dapagliflozin did not show any toxicity in the reported study where healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

### **Metformin**

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

## **5. Pharmacological properties**

### **5.1 Mechanism of Action**

## **Sitagliptin**

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 reported 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.

## **Dapagliflozin**

Dapagliflozin is a highly potent ( $K_i$ : 0.55 nM), selective and reversible inhibitor of SGLT2.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF and DAPA-CKD studies.

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose and/or low GFR, dapagliflozin has a low propensity to cause hypoglycaemia, as the amount of filtrated glucose is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.

The SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

## **Metformin**



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 3 mechanisms:

- 1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- 2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- 3) and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

## 5.2 Pharmacodynamic properties

### Sitagliptin

Pharmacotherapeutic group: Drugs used in diabetes, Dipeptidyl peptidase 4 (DPP-4) inhibitors, ATC code: A10BH01.

#### *Clinical efficacy and safety*

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

Two studies were conducted to evaluate the efficacy and safety of sitagliptin monotherapy. Treatment with sitagliptin at 100 mg once daily as monotherapy provided significant improvements in HbA1c, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (2-hour PPG), compared to placebo in two studies, one of 18- and one of 24-weeks duration. Improvement of 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. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.

Sitagliptin 100 mg once daily provided significant improvements in glycaemic parameters compared with placebo in two 24-week studies of sitagliptin as add-on therapy, one in combination with metformin and one in combination with pioglitazone. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In these studies there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

A 24-week placebo-controlled reported study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride alone or glimepiride in combination with metformin. The addition of sitagliptin to either glimepiride alone or to glimepiride and metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight compared to those given placebo.

A 26-week placebo-controlled reported study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of pioglitazone and metformin. The addition of sitagliptin to pioglitazone and metformin provided significant improvements in glycaemic parameters. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. The incidence of hypoglycaemia was also similar in patients treated with sitagliptin or placebo.

A 24-week placebo-controlled reported study was designed to evaluate the efficacy and safety of

sitagliptin (100 mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

In a 24-week placebo-controlled reported 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.

A 24-week active (metformin)-controlled reported study was designed to evaluate the efficacy and safety of sitagliptin 100 mg once daily (N=528) compared to metformin (N=522) in patients with inadequate glycaemic control on diet and exercise and who were not on anti-hyperglycaemic therapy (off therapy for at least 4 months). The mean dose of metformin was approximately 1,900 mg per day. The reduction in HbA1c from mean baseline values of 7.2 % was -0.43 % for sitagliptin and -0.57 % for metformin (Per Protocol Analysis). The overall incidence of gastrointestinal adverse reactions considered as drug-related in patients treated with sitagliptin was 2.7 % compared with 12.6 % in patients treated with metformin. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 1.3 %; metformin, 1.9 %). Body weight decreased from baseline in both groups (sitagliptin, -0.6 kg; metformin -1.9 kg).

In a reported study comparing the efficacy and safety of the addition of sitagliptin 100 mg once daily or glipizide (a sulphonylurea) in patients with inadequate glycaemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbA1c. The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of  $\leq 5$  mg/day throughout the study. However, more patients in the sitagliptin group discontinued due to lack of efficacy than in the glipizide group. Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glipizide (-1.5 vs. +1.1 kg). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycaemia in the sitagliptin group (4.9 %) was significantly lower than that in the glipizide group (32.0 %).

A 24-week placebo-controlled reported study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin therapy. Baseline HbA1c was 8.74 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. At Week 24, the increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in HbA1c in patients treated with sitagliptin and insulin (with or without metformin) was -1.31 % compared to -0.87 % in patients treated with placebo and insulin (with or without metformin), a difference of -0.45 % [95 % CI: -0.60, -0.29]. The incidence of hypoglycaemia was 25.2 % in patients treated with sitagliptin and insulin (with or without metformin) and 36.8 % in patients treated with placebo and insulin (with or without metformin). The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.4 vs. 19.1 %). There was no difference in the incidence of severe hypoglycaemia.

A reported study comparing sitagliptin at 25 or 50 mg once daily to glipizide at 2.5 to 20 mg/day

was conducted in patients with moderate to severe renal impairment. This study involved 423 patients with chronic renal impairment (estimated glomerular filtration rate < 50 mL/min). After 54 weeks, the mean reduction from baseline in HbA1c was -0.76 % with sitagliptin and -0.64 % with glipizide (Per-Protocol Analysis). In this study, the efficacy and safety profile of sitagliptin at 25 or 50 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia in the sitagliptin group (6.2 %) was significantly lower than that in the glipizide group (17.0 %). There was also a significant difference between groups with respect to change from baseline body weight (sitagliptin -0.6 kg; glipizide +1.2 kg).

Another reported study comparing sitagliptin at 25 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in 129 patients with ESRD who were on dialysis. After 54 weeks, the mean reduction from baseline in HbA1c was -0.72 % with sitagliptin and -0.87 % with glipizide. In this study, the efficacy and safety profile of sitagliptin at 25 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 6.3 %; glipizide, 10.8 %).

In another reported study involving 91 patients with type 2 diabetes and chronic renal impairment (creatinine clearance < 50 mL/min), the safety and tolerability of treatment with sitagliptin at 25 or 50 mg once daily were generally similar to placebo. In addition, after 12 weeks, the mean reductions in HbA1c (sitagliptin -0.59 %; placebo -0.18 %) and FPG (sitagliptin -25.5 mg/dL; placebo -3.0 mg/dL) were generally similar to those observed in other monotherapy studies in patients with normal renal function.

The TECOS was a randomised study in 14,671 patients in the intention-to-treat population with an HbA1c of  $\geq 6.5$  to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was  $\geq 30$  and < 50 mL/min/1.73 m<sup>2</sup>) or placebo (7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 m<sup>2</sup> were not to be enrolled in the study. The study population included 2,004 patients  $\geq 75$  years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m<sup>2</sup>).

Over the course of the study, the overall estimated mean (SD) difference in HbA1c between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27);  $p < 0.001$ .

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes.

#### Paediatric population

A 54-week, double-blind reported study was conducted to evaluate the efficacy and safety of sitagliptin 100 mg once daily in paediatric patients (10 to 17 years of age) with type 2 diabetes who were not on anti hyperglycaemic therapy for at least 12 weeks (with HbA1c 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA1c 7% to 10%). Patients were randomised to sitagliptin 100 mg once daily or placebo for 20 weeks.

Mean baseline HbA1c was 7.5%. Treatment with sitagliptin 100 mg did not provide significant

improvement in HbA1c at 20 weeks. The reduction in HbA1c in patients treated with sitagliptin (N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3).

### **Dapagliflozin**

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/L (-0.87 to -0.33 mg/dL).

### **Metformin**

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

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, LDL cholesterol and triglyceride levels.

## **5.3 Pharmacokinetic properties**

### **Sitagliptin and Dapagliflozin**

#### *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 Mm.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).

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations ( $C_{max}$ ) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin  $C_{max}$  and AUC values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration with a high-fat meal decreased dapagliflozin  $C_{max}$  by up to 50% and prolonged  $T_{max}$  by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. Hence, Dapagliflozin can be administered

with or without food.

### 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 %).

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 liters.

### 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 reported *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.

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans

### 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.

The mean plasma terminal half-life ( $t_{1/2}$ ) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 mL/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [<sup>14</sup>C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

### Linearity

Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

### **Characteristics in patients**

The pharmacokinetics of sitagliptin and Dapagliflozin 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 ( $\text{GFR} \geq 60$  to  $< 90$  mL/min) and patients with moderate renal impairment ( $\text{GFR} \geq 45$  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 ( $\text{GFR} \geq 30$  to  $< 45$  mL/min), and approximately 4-fold in patients with severe renal impairment ( $\text{GFR} < 30$  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).

At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of haemodialysis on dapagliflozin exposure is not known. The effect of reduced renal function on systemic exposure was evaluated in a population pharmacokinetic model. Consistent with previous results, model predicted AUC was higher in patients with chronic kidney disease compared with patients with normal renal function, and was not meaningfully different in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes.

### 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.

In reported study subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean  $C_{\text{max}}$  and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically

meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean  $C_{max}$  and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

#### 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.

There is no reported clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

#### 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.

Pharmacokinetics and pharmacodynamics (glucosuria) in children with type 2 diabetes mellitus aged 10-17 years were similar to those observed in adults with type 2 diabetes mellitus.

#### Gender

The mean dapagliflozin AUC<sub>ss</sub> in reported study females was estimated to be about 22% higher than in males.

#### Race

There were no reported clinically relevant differences in systemic exposures between White, Black or Asian races.

#### Body weight

Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.

#### *Other patient characteristics with sitagliptin*

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 reported 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 hydrochloride tablet, maximum plasma concentration ( $C_{max}$ ) is reached in approximately 2.5 hours ( $t_{max}$ ). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride 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 recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C<sub>max</sub>) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings 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 volume of distribution (V<sub>d</sub>) ranged between 63-276 l.

#### *Metabolism:*

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 hours.

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.

Characteristics in specific group of patients

#### *Renal impairment*

The available data in persons with moderate renal insufficiency are sparse and no reliable estimation of systemic metformin exposure in this subgroup could be made compared to persons with normal renal function. Therefore, dose adjustment should be based on clinical efficacy / tolerability.

#### *Paediatric population*

Single dose study: After single doses of metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults. Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in pediatric patients the peak plasma concentration (C<sub>max</sub>) and systemic exposure (AUC<sub>0-t</sub>) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

## **6. Nonclinical properties**

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

#### **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).

### **Dapagliflozin**

In reported non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

#### *Reproductive and developmental toxicity*

Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a reported juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were  $\geq 15$  times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a reported separate study of pre- and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin

exposures were 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses  $\geq 15$  mg/kg/day (associated with pup exposures that are  $\geq 29$  times the human values at the maximum recommended human dose). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The no observed adverse effect level (NOAEL) for developmental toxicity, the lowest dose tested, is associated with a maternal systemic exposure multiple that is approximately 19 times the human value at the maximum recommended human dose.

In additional reported studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested; the highest dose tested is associated with a systemic exposure multiple of approximately 1,191 times the maximum recommended human dose. In rats, dapagliflozin was neither embryo-lethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose.

### Metformin

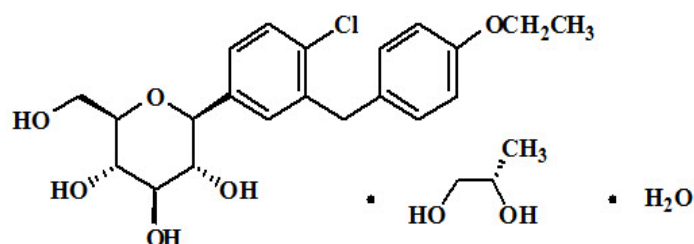
Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

## 7. Description

### Dapagliflozin

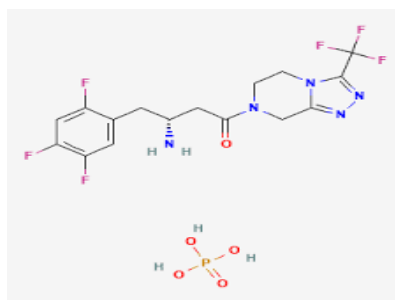
Dapagliflozin propanediol monohydrate is ((2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxane-3,4,5-triol;(2S)-propane-1,2-diol;hydrate. The molecular formula is  $C_{24}H_{35}ClO_9$  and the molecular weight is 503.0. The chemical structure of Dapagliflozin propanediol monohydrate is:

The Structural formula is:



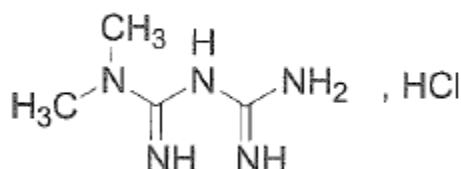
### Sitagliptin

Sitagliptin Phosphate Monohydrate is (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4]triazolo [4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one; phosphoric acid. The molecular formula is  $C_{16}H_{18}F_6N_5O_5P$  and the molecular weight is 505.31. The chemical structure of Sitagliptin Phosphate Monohydrate is:



### Metformin Hydrochloride

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



### STALIX DM 10/100/1000

Dapagliflozin, Sitagliptin & Metformin Hydrochloride Extended Release Tablets are Blue colored, capsule shape, biconvex, film coated tablets, plain on both sides.

The excipients used are Colloidal Silicone Dioxide, Microcrystalline Cellulose, Mannitol, Indigo carmine Aluminum lake, Povidone K 30, Purified water, Croscarmellose Sodium, Magnesium Stearate, Hydroxypropylmethyl Cellulose, Isopropyl alcohol, Di calcium Phosphate Anhydrous, Instacoat aqua II Blue. **STALIX DM 10/100/500**

Dapagliflozin, Sitagliptin & Metformin Hydrochloride Extended Release Tablets are Peach colored, capsule shape, biconvex, film coated tablets, plain on both sides.

The excipients used are Colloidal Silicone Dioxide, Microcrystalline Cellulose, Mannitol, Iron oxide yellow, Povidone K 30, Purified water, Croscarmellose Sodium, Magnesium Stearate, Hydroxypropylmethyl Cellulose, Isopropyl alcohol, Di calcium Phosphate Anhydrous, Instacoat aqua II Peach.

## 8. Pharmaceutical particulars

### 8.1 Incompatibilities

Not applicable

### 8.2 Shelf-life

Do not use later than date of expiry.

### 8.3 Packaging information

Dapagliflozin, Sitagliptin and Metformin Hydrochloride Extended Release Tablets is available in pack of 10 tablets.

#### 8.4 Storage and handing instructions

Store below 30° C,

Keep out of reach of children

Tablets Should be swallowed whole & not chewed or crushed.

#### 9. Patient Counselling Information

##### Package leaflet: Information for the user

##### STALIX DM

(10+100+1000) (10+100+500)

##### Dapagliflozin , Sitagliptin and Metformin Hydrochloride Extended Release 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 DM and what it is used for

9.2 What you need to know before you take STALIX DM

9.3 How to take STALIX DM

9.4 Possible side effects

9.5 How to store STALIX DM

9.6 Contents of the pack and other information

#### 9.1 What STALIX DM is and what it is used for

STALIX DM contains Dapagliflozin , Sitagliptin and Metformin Hydrochloride Extended Release Tablets.

It is used for the treatment of type 2 diabetes mellitus inadequately controlled on Metformin monotherapy.

#### 9.2 What you need to know before you take STALIX DM

If you are allergic to sitagliptin, metformin and Dapagliflozin or any of the other ingredients of this medicine.

**Do not take STALIX DM** if 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 STALIX DM.

##### Warnings and precautions

Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving STALIX DM.

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 DM.

Tell your doctor if you have or have had:

- a disease of the pancreas (such as pancreatitis)
- 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.

- type 1 diabetes
- diabetic ketoacidosis (a complication of diabetes with high blood sugar, rapid weight loss, nausea or vomiting)
- any past or present kidney problems
- an allergic reaction to STALIX DM

This medicine is unlikely to cause low blood sugar because it does not work when your blood sugar is low. However, when this medicine is used in combination with a sulphonylurea medicine or with insulin, low blood sugar (hypoglycaemia) can occur. Your doctor may reduce the dose of your sulphonylurea or insulin medicine.

#### *Diabetic ketoacidosis:*

- If you have diabetes and experience feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat or rapid weight loss.
- The above symptoms could be a sign of “diabetic ketoacidosis” – a rare but serious, sometimes life-threatening problem you can get with diabetes because of increased levels of “ketone bodies” in your urine or blood, seen in tests.
- The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness.
- When you are treated with Dapagliflozin, diabetic ketoacidosis can occur even if your blood sugar is normal.

If you suspect you have diabetic ketoacidosis, contact a doctor or the nearest hospital straight away and do not take this medicine.

#### *Necrotising fasciitis of the perineum:*

- Talk to your doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotising fasciitis of the perineum or Fournier’s gangrene which destroys the tissue under the skin. Fournier’s gangrene has to be treated immediately.

#### Metformin:

Do not take Metformin Film-coated Tablets:

- if you are allergic to metformin or any of the Other ingredients of this medicine
- if you have liver problems.

If you have severely reduced kidney function. If you have uncontrolled diabetes, with, for example, 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 lost too much water from your body (dehydration), due to long-lasting or severe diarrhoea, or if you have vomited several times in a row. Dehydration may lead to kidney problems, which can put you at risk for lactic acidosis (see Warnings and precautions’)

If you have a severe infection, such as an infection affecting your lungs or bronchial system or your kidney. Severe infections may lead to kidney problems, which can put you at risk for lactic acidosis (see ‘Warnings and precautions”).

if you are treated for acute heart failure or have recently had a heart attack, have severe Problems with your circulation (such as shock) or have breathing difficulties. This may lead to a lack in oxygen supply to tissue which can put you at risk for lactic acidosis (see ‘Warnings and precautions’).

If you drink a lot of alcohol.

If any of the above applies to you, talk to your Doctor before you start taking this medicine. Make sure you ask your doctor for advice if: you need to have an examination such as Xray or scan involving the injection of contrast medicines that contain iodine into your blood stream.

You need to have major surgery.

You must stop taking this medicine for a certain period of time before and after the examination or the surgery. Your doctor will decide whether you need any other treatment during this time. It is important that you follow your doctor’s instructions precisely.

### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Metformin Film-coated Tablets.

#### **Risk of lactic acidosis**

Metformin Film-coated Tablets 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, 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 Metformin Film-coated Tablets 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 Metformin Film-coated Tablets 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

Stomach ache (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

If you need to have major surgery you must stop taking this medicine during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Metformin Film coated Tablets. Metformin Film-coated Tablets on its own do not cause hypoglycaemia (a blood glucose level which is too low). However, if you take Metformin Film-coated Tablets together with other medicines to treat diabetes (such as sulphonylureas, Insulin or meglitinides) there is a risk of hypoglycaemia. If you experience symptoms of hypoglycaemia such as weakness, dizziness, increased sweating, fast heart beating, vision disorders or difficulty in concentration, it usually helps to eat or drink something containing sugar.

During treatment with this medicine, 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.

Metformin:

Children and adolescents Treatment of children between 10 and 12 years of age is only recommended on specific advice from your doctor, as experience in this age group is limited

### **Other medicines and STALIX DM**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking digoxin (a medicine used to treat irregular heartbeat and other heart problems). The level of digoxin in your blood may need to be checked if taking with STALIX DM.

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Especially tell your doctor:

- if you are taking a medicine used to remove water from the body (diuretic).
- if you are taking other medicines that lower the amount of sugar in your blood such as insulin or a "sulphonylurea" medicine. Your doctor may want to lower the dose of these other medicines, to prevent you from getting low blood sugar levels (hypoglycaemia).

You may need more frequent blood glucose and kidney function tests or your doctor may need to adjust the dosage of Metformin Film-coated Tablets. 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 Metformin Film-coated Tablets before or at the time of injection. Your doctor will decide when you must stop and when to restart your treatment With Metformin Film-coated Tablets.

It is especially important to mention to your doctor if you are taking:

- 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)
- Beta-2 agonists such as salbutamol or Terbutaline (used to treat asthma).
- Corticosteroids (used to treat a variety of conditions, such as severe inflammation Of the skin or in asthma).
- Medicines that may change the amount of Metformin in your blood, especially if you Have reduced kidney function (such as verapamil, Rifampicin, cimetidine, dolutegravir, ranolazine, Trimethoprim, vandetanib, Isavuconazole, Crizotinib, olaparib).
- Other medicines used to treat diabetes. Metformin Film-coated Tablets with alcohol Avoid excessive alcohol intake while taking Metformin Film-coated Tablets 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.

During pregnancy, you need insulin to treat your diabetes. Tell your doctor if you are, you think you might be or are planning to become pregnant, so that he or she may change your treatment.

This medicine is not recommended if you are breast-feeding or if you are planning to breastfeed your baby.

### **Driving and using machines**

Metformin Do not Cause hypoglycaemia (a blood glucose level which is too low). This means that it will not affect your ability to drive or use machines.

However, take special care if you take Metformin Film-coated Tablets together with other medicines to treat diabetes that can cause hypoglycaemia (such as sulphonylureas, insulin, meglitin des). Symptoms of hypoglycaemia include weakness. Dizziness, increased sweating, fast heartbeat, vision disorders or difficulty in concentration. Do not drive or use machines if you start to feel these symptoms.

## **9.3 How to take STALIX DM**

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

Your doctor will prescribe the strength that is right for you.

Taking this medicine

- Swallow the tablet whole with half a glass of water.
- You can take your tablet with or without food.
- You can take the tablet at any time of the day. However, try to take it at the same time each day. This will help you to remember to take it.

Your doctor may prescribe this medicine alone or with certain other medicines that lower blood



sugar.

Diet and exercise can help your body use its blood sugar better. It is important to stay on the diet and exercise recommended by your doctor while taking STALIX DM.

### **If you take more STALIX DM than you should**

If you take more than the prescribed dosage of this medicine, contact your doctor immediately.

### **If you forget to take STALIX DM**

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 DM**

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

### **Use in children and adolescents**

Children 10 years and over and adolescents usually start with 500 mg or 850 mg Metformin Film-coated Tablets once a day. The maximum Daily dose is 2000 mg taken as 2 or 3 divided Doses.

## **9.4 Possible side effects**

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

STOP taking STALIX DM 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).

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).

### ***Dapagliflozin***

Contact a doctor or the nearest hospital straight away if you have any of the following side effects:

- angioedema, seen very rarely (may affect up to 1 in 10,000 people).

These are signs of angioedema:

- swelling of the face, tongue or throat
- difficulties swallowing
- hives and breathing problems
- diabetic ketoacidosis - this is rare in patients with type 2 diabetes (may affect up to 1 in 1,000 people).

These are the signs of diabetic ketoacidosis:

- increased levels of “ketone bodies” in your urine or blood
- feeling sick or being sick
- stomach pain
- excessive thirst
- fast and deep breathing
- confusion
- unusual sleepiness or tiredness
- a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat
- rapid weight loss.

This may occur regardless of blood sugar level. Your doctor may decide to temporarily or permanently stop your treatment with Dapagliflozin.

- necrotising fasciitis of the perineum or Fournier's gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus, seen very rarely.

Stop taking Dapagliflozin and see a doctor as soon as possible if you notice any of the following serious side effects:

- urinary tract infection, seen commonly (may affect up to 1 in 10 people).

These are signs of a severe infection of the urinary tract:

- fever and/or chills
- burning sensation when passing water (urinating)
- pain in your back or side.

Although uncommon, if you see blood in your urine, tell your doctor immediately.

Contact your doctor as soon as possible if you have any of the following side effects:

- low blood sugar levels (hypoglycaemia), seen very commonly (may affect more than 1 in 10 people) in patients with diabetes taking this medicine with a sulphonylurea or insulin.

These are the signs of low blood sugar:

- shaking, sweating, feeling very anxious, fast heart beat
- feeling hungry, headache, change in vision
- a change in your mood or feeling confused.

Your doctor will tell you how to treat low blood sugar levels and what to do if you get any of the signs above.

### **Other side effects when taking Dapagliflozin:**

#### *Common*

- genital infection (thrush) of your penis or vagina (signs may include irritation, itching, unusual discharge or odour)
- back pain
- passing more water (urine) than usual or needing to pass water more often
- changes in the amount of cholesterol or fats in your blood (shown in tests)
- increases in the amount of red blood cells in your blood (shown in tests)
- decreases in creatinine renal clearance (shown in tests) in the beginning of treatment
- dizziness
- rash

#### *Uncommon (may affect up to 1 in 100 people)*

- loss of too much fluid from your body (dehydration, signs may include very dry or sticky mouth, passing little or no urine or fast heartbeat)
- thirst
- constipation
- awakening from sleep at night to pass urine
- dry mouth

- weight decreased
- increases in creatinine (shown in laboratory blood tests) in the beginning of treatment
- increases in urea (shown in laboratory blood tests)

### **Metformin**

Like all medicines, this medicine can cause side effects, although not everybody gets them. Metformin Film-coated Tablets may cause a very rare (may affect up to 1 in 10,000 people), but very serious side effect called lactic acidosis (see section Warnings and precautions). If this happens you must **stop taking Metformin Film-coated Tablets and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

Other side effects which may occur:

#### **Very common** (may affect more than 1 in 10 people)

Digestive problems such as feeling sick (nausea), being sick (vomiting), diarrhoea, bellyache (abdominal pain) and loss of appetite.

These side effects most often happen at the beginning of the treatment with metformin. It helps if you spread the doses over the day and if you take this medicine with or straight after a meal. **If symptoms continue, stop taking Metformin Film-coated Tablets and talk to your doctor.**

#### **Common** (may affect up to 1 in 10 people)

changes in taste.

#### **Very rare** (may affect up to 1 in 10,000 people)

lactic acidosis. This is a very rare but serious complication particularly if your kidneys are not working properly. Symptoms of lactic acidosis are non-specific (see section “Warning and precautions”).

Abnormalities in liver function tests or hepatitis (inflammation of the liver; this may cause tiredness, loss of appetite, weight loss, with or without yellowing of the skin or whites of the eyes). If this happens to you, **stop taking Metformin Film-coated Tablets and talk to your doctor.**

Skin reactions such as redness of the skin (erythema), itching or an itchy rash (hives).

Low vitamin B levels in the blood

### **Additional side effects in children and adolescents**

Limited data in children and adolescents showed that adverse events were similar in nature and severity to those reported in adults.

### **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.

## **9.5 How to store STALIX DM**

Store below 30° C.

Keep out of reach of children

Tablets Should be swallowed whole & not chewed or crushed.

## **9.6 Contents of the pack and other information**

### **What STALIX DM contains**

Stalix DM contain Dapagliflozin , Sitagliptin and Metformin Hydrochloride Extended Release Tablets.

STALIX DM (10+100+1000 mg)

The excipients used are Colloidal Silicone Dioxide, Microcrystalline Cellulose, Mannitol, Indigo carmine Aluminum lake, Povidone K 30, Purified water, Croscarmellose Sodium, Magnesium Stearate, Hydroxypropylmethyl Cellulose, Isopropyl alcohol, Di calcium Phosphate Anhydrous, , Instacoat aqua II Blue.

STALIX DM (10+100+500 mg)

The excipients used are Colloidal Silicone Dioxide, Microcrystalline Cellulose, Mannitol, Iron oxide yellow, Povidone K 30, Purified water, Croscarmellose Sodium, Magnesium Stearate, Hydroxypropylmethyl Cellulose, Isopropyl alcohol, Di calcium Phosphate Anhydrous, Instacoat aqua II Peach.

### **What STALIX DM looks like and contents of the pack**

Dapagliflozin, Sitagliptin and Metformin Hydrochloride Extended Release Tablets is available in pack of 10 tablets.

## **10. Details of manufacturer**

Exemed Pharmaceuticals

Plot No. 133/1 & 133/2, G.I.D.C.,

Selvas Road, Vapi – 396195,

Gujarat, INDIA

## **11. Details of permission or licence number with date**

Mfg. Lic. No. G/25/2011 issued on 18.10.2022

## **12. Date of revision**

NA

### **MARKETED BY**



TORRENT PHARMACEUTICALS LTD.

**IN/Stalix DM/10+100+1000 mg/10+100+500 mg/Mar-23/01/PI**