

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DAPEFY SM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION DAPEFY SM

Each Film coated tablet contains:

Dapagliflozin Propanediol monohydrate

Equivalent to Dapagliflozin.....10mg

Sitagliptin Phosphate Monohydrate

Equivalent to Sitagliptin.....100mg

Metformin Hydrochloride.....1000mg

Excipient Of known effect

Each tablet contains 91.1 mg Anhydrous Lactose

For excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Extended-Release Film Coated tablet

Light yellow to yellow colored capsule shaped film coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DAPEFY SM is indicated in adults for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise.

4.2 Posology and method of administration

Posology

The dosage of dapagliflozin/sitagliptin/metformin should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin, 2000 mg metformin and 100 mg sitagliptin.

Initial combination therapy or maintenance of combination therapy should be individualized and left to the discretion of the health care provider.

The therapy should be initiated with one tablet of

Dapagliflozin/Sitagliptin/Metformin 10/100/500 mg once daily with the evening meal

Dapagliflozin/Sitagliptin/Metformin are intended for patients who are already treated with metformin tablets (prolonged or immediate release).

In patients already treated with metformin tablets, the starting dose of metformin in Dapagliflozin/Sitagliptin/Metformin should be equivalent to the daily dose of metformin immediate release tablets already being taken.

After 10 to 15 days dose adjustment on the basis of blood glucose measurements is recommended (OGTT and/or FPG and/or HbA1c values to be within the normal range).

It is recommended to regularly monitor (every 3-6 months) the glycaemic status (OGTT and/or FPG and/or HbA1c value) as well as the risk factors to evaluate whether treatment needs to be continued, modified or discontinued.

Special population

Pediatric population

DAPEFY SM should not be used in children less than 18 years of age.

Elderly population

No dose adjustment is recommended based on age. Assessment of renal function is recommended prior to initiating Dapagliflozin/Sitagliptin/Metformin and periodically thereafter.

Dapagliflozin/sitagliptin/metformin is not recommended in patients of 75 years and older with type 2 diabetes.

Hepatic impairment

Dapagliflozin/Sitagliptin/Metformin should not be used in patients with hepatic impairment.

Renal impairment

A GFR should be assessed before initiation of treatment with Dapagliflozin/Sitagliptin/Metformin tablets containing medicinal products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

– For patients with mild renal impairment (glomerular filtration rate [GFR] $\geq$ 60 to

< 90 mL/min), no dose adjustment is required. Dose reduction may be considered in relation to declining renal function.

– For patients with moderate renal impairment (GFR $\geq$ 45 to < 60 mL/min), no dosage adjustment is required. Factors that may increase the risk of lactic acidosis (**see section 4.4**) should be reviewed before considering initiation of Metformin in patients with GFR < 60 mL/min. The starting dose is at most half of the maximum daily dose of metformin.

Method of Administration

Oral use

DAPEFY SM should be administered with food (see **sections 5.1 & 5.2**).

4.3 **Contraindications**

DAPEFY SM is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients of the formulation.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (GFR < 30 mL/min).
- Acute conditions with the potential to alter renal function such as:
 - dehydration,
 - severe infection,
 - shock
- 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**

Diabetic ketoacidosis

Dapagliflozin/Sitagliptin/Metformin tablets should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Dapagliflozin/Sitagliptin/Metformin tablets

The risk of diabetic ketoacidosis (DKA) 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/Sitagliptin/Metformin tablets 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. Before initiating Dapagliflozin/Sitagliptin/Metformin tablets, 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.

Restarting dapagliflozin/sitagliptin treatment in patients experiencing a DKA while on Dapagliflozin/Sitagliptin/Metformin tablets treatment is not recommended.

Renal impairment

Dapagliflozin/Sitagliptin/ Metformin is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m², severe renal impairment, end-stage renal disease (ESRD) or patients on dialysis. Assessment of renal function is recommended prior to initiating.

Dapagliflozin/Sitagliptin/Metformin tablets and periodically thereafter.

In patients with moderate renal impairment (eGFR < 60 mL/min/1.73 m²), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo.

Hepatic impairment

This medicinal product must not be used in patients with hepatic impairment (**See section 4.3**).

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. 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 (**see section 4.7**).

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (**see section 4.7**). 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

Elderly patients (≥ 65 years) 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 (**see sections 4.4 and 4.7**).

Due to the limited therapeutic efficacy data in the reduction of risk or delay of type 2 diabetes in patients 75 years and older, metformin initiation is not recommended in these patients.

Cardiac failure

Experience with dapagliflozin in NYHA class IV is limited.

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

For patients with acute and unstable heart failure, metformin is contraindicated (see **section 4.3**).

Chronic kidney disease

There is no reported 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 reported 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.

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

reported 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

The rates of hypoglycaemia reported with sitagliptin as monotherapy and as part of combination therapy with medicinal products not known to cause hypoglycaemia (i.e. metformin and/or a PPAR γ agonist), were similar to rates in patients taking placebo. Hypoglycaemia has been reported 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.

Metformin alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulphonylureas or meglitinides).

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 some reports occurring after the first dose. If a hypersensitivity reaction is suspected, sitagliptin should be discontinued. Other potential causes for the event should be assessed, and alternative treatment for diabetes initiated.

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.

Lactic acidosis

Lactic acidosis, a very rare, but serious, metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin

accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe 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 anti hypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (**see sections 4.3 and 4.5**).

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

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, **see section 4.5**.

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 re-evaluated and found to be stable.

Other precautions

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

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

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

The tablet shells may be present in the faeces. Patients should be advised that this is normal.

Excipients

The medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

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 (see **section 4.7**).

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyl transferase 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 co-administered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin

Interaction studies reported 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 co-administration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was reported, 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 co-administration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was reported, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

Dapagliflozin may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after dapagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

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

Interaction studies have only been reported in adults.

Sitagliptin

Effects of other medicinal products on sitagliptin

For sitagliptin the risk for clinically meaningful interactions by co-administered medicinal products is low.

The 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 is not reported.

In vitro transport studies reported 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

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

Effects of sitagliptin on other medicinal products

Digoxin

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

The reported *in vitro* data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. 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*.

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 imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see **section 4.4**.

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 other drug 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 **Fertility, pregnancy and lactation**

Dapagliflozin

Pregnancy

There are no reported data from the use of dapagliflozin in pregnant women. The

reported studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see **section 5.3**). 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.

Breast-feeding

It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have reported excretion of dapagliflozin/metabolites in milk, as well as pharmacologically mediated effects in nursing offspring (see **section 5.3**). A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

Fertility

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

Sitagliptin

Pregnancy

There are no reported adequate data from the use of sitagliptin in pregnant women. Reported studies in animals have shown reproductive toxicity at high doses (see **section 5.3**). The potential risk for humans is unknown. Due to lack of human data, sitagliptin should not be used during pregnancy.

Breast-feeding

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

Fertility

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

Metformin

Pregnancy

Uncontrolled hyperglycaemia in the periconceptional phase and during pregnancy is associated with increased risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality. It is important to maintain blood glucose levels as close to normal as possible throughout pregnancy, to reduce the risk of adverse hyperglycaemia-related outcomes to the mother and her child.

Metformin crosses the placenta with levels that can be as high as maternal concentrations.

A large amount of reported data on pregnant women (more than 1000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) indicates no increased risk of congenital abnormalities nor fetoneonatal toxicity after exposure to metformin in the periconceptional phase and/or during pregnancy.

There is limited and inconclusive reported evidence on the metformin effect on the long-term weight outcome of children exposed in utero. Metformin does not appear to affect motor and social development up to 4 years of age in children exposed during pregnancy although data on long term outcomes are limited.

If clinically needed, the use of metformin can be considered during pregnancy and in the periconceptional phase as an addition or an alternative to insulin.

Breast-feeding

Metformin is excreted into human breast milk. No adverse effects were reported in breastfed newborns/infants. However, as only limited reported 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 breast-feeding and the potential risk to adverse effect on the child.

Fertility

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

Dapagliflozin/sitagliptin/Metformin tablets has no or negligible influence on the ability to drive and use machines.

However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported for sitagliptin.

Patients should be alerted to the risk of hypoglycaemia when dapagliflozin/sitagliptin/metformin tablets are used in combination with a sulphonylurea, insulin or meglinitides.

4.8 Undesirable effects

Dapagliflozin

Summary of the safety profile

Type 2 diabetes mellitus

In reported clinical studies the most frequently reported adverse reactions in patients with type 2 diabetes were genital infections.

Heart failure

The safety of dapagliflozin was reported in patients with heart failure with reduced ejection fraction, including patients with or without type 2 diabetes mellitus and patients with reduced renal function (eGFR $\geq$ 25 mL/min/1.73 m² to eGFR $\geq$ 30 mL/min/1.73 m²). The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

Chronic kidney disease

The overall safety profile of dapagliflozin in patients with chronic kidney disease (eGFR $\geq$ 25 to $\leq$ 75 mL/min/1.73 m²) was consistent with the known safety profile of dapagliflozin.

Tabulated list of adverse reactions

The following adverse reactions have been reported in the placebo-controlled clinical studies and post-marketing surveillance. None were reported 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 reported data).

Table: Adverse reactions reported in placebo-controlled clinical studies^a and post-marketing experience

System organ class	Very common	Common[*]	Uncommon[*]	Rare	Very rare
<i>Infections and infestations</i>		Vulvovaginitis, balanitis and related genital infections ^{*,b,c} Urinary tract infection ^{*,b,d}	Fungal infection ^{**}		Necrotising fasciitis of the perineum (Fournier's gangrene) ^{b,i}
<i>Metabolism and nutrition disorders</i>	Hypoglycaemia (when used with SU or insulin) ^b		Volume depletion ^{b,e} Thirst ^{**}	Diabetic ketoacidosis (when	

				used in type 2 diabetes	
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System organ class	Very comm on	Common*	Uncommo n* *	Rare	Very rare
				mellitus) ^b ,i, k	
<i>Nervous system disorders</i>		Dizziness			
<i>Gastrointe stin al disorders</i>			Constipati on ** Dry mouth**		
<i>Skin and subcutane ous tissue disorders</i>		Rash ^j			Angioedema
<i>Musculosk elet al and connective tissue disorde rs</i>		Back pain*			
<i>Renal and urinary disorders</i>		Dysuria Polyuria*, ^f	Nocturia**		Tubulointer stiti al nephritis
<i>Reproducti ve system and breast disorders</i>			Vulvovagi na l pruritus** Pruritus genital**		
<i>Investigatio ns</i>		Haematoc rit increased ^g Creatinine renal clearance decreased during initial treatment ^b Dyslipidae	Blood creatinin e increased during initial treatment **, ^b Blood urea increased ** Weight decreased		

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^a The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

^b See corresponding subsection below for additional information.

^c 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.

^d 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.

^e Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

^f Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

^g 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.

^h 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%.

ⁱ See **section 4.4**.

^j Adverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in reported clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In reported 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.

^k Reported in the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.

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

**Reported as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo

Description of selected adverse reactions for dapagliflozin

Vulvovaginitis, balanitis and related genital infections

In reported pooled safety study 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.

Few cases of serious adverse events of genital infections were reported for dapagliflozin as compared to placebo.

In a reported clinical study no patient reported serious adverse events of genital infections in the dapagliflozin group as compared to single patient in the placebo group. There were 0.3% patients with adverse events leading to discontinuations due to genital infections in the dapagliflozin group and none in the placebo group. In another clinical study, < 0.1% patient in each treatment group reported a serious adverse event of genital infections. There were 0.1% patients with adverse events leading to discontinuations due to genital infection in the dapagliflozin group and none in the placebo group.

Similar evidence of very few cases of patients (0.1%) with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group was also reported in another study. There were 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 (see **section 4.4**).

In a reported study with type 2 diabetes mellitus patients and a median exposure time of 48 months, less cases of Fournier's gangrene was reported in the dapagliflozin group as compared to placebo.

Hypoglycaemia

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

For reported 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 reported 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 (see **section 4.5**).

In an add-on to reported 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 reported 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 a study, no increased risk of major hypoglycaemia was reported with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 0.7% patients treated with dapagliflozin and 1.0% patients treated with placebo.

In a study, major events of hypoglycaemia were reported in 0.2% patients in both the dapagliflozin and placebo treatment groups. In another study, major events of hypoglycaemia were reported in 0.2% patients in the dapagliflozin group and 0.2% in the placebo group. Major events of hypoglycaemia were only reported in patients with type 2 diabetes mellitus.

In a study, major events of hypoglycaemia were reported in 0.7% patients in the dapagliflozin group and 1.3% patients in the placebo group and reported only in patients with type 2 diabetes mellitus.

Volume depletion

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 (see **section 4.4**).

In a reported study the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 2.5% and 2.4% in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 0.9% and 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 (ACEI)/angiotensin II type 1 receptor blockers (ARB) use. In patients with eGFR < 60 mL/min/1.73 m² at baseline, there were more events of serious adverse events suggestive of volume depletion in the dapagliflozin group than in the placebo group.

In a reported study, the numbers of patients with events suggestive of volume depletion were 7.2% in the dapagliflozin group and 6.5% in the placebo group. There were fewer patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group (1.0%) compared with the placebo group (1.6%). Results were similar irrespective of presence of diabetes at baseline and baseline eGFR. In a reported study, the numbers of patients with serious events of symptoms suggestive of volume depletion were 1.1% in the dapagliflozin group and 1.0% in the placebo group.

In a reported study, the numbers of patients with events suggestive of volume depletion were 5.6% in the dapagliflozin group and 3.9% in the placebo group. There were 0.7% patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group and 0.7% patients in the placebo group.

Diabetic ketoacidosis in type 2 diabetes mellitus

In a reported study, with a median exposure time of 48 months, events of DKA were doubled in the dapagliflozin 10 mg group as compared to the placebo group. The events occurred evenly distributed over the study period. Of the patients with DKA events in the dapagliflozin group, 81.5 % had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see **section 4.4**).

In a 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 another study, events of DKA were reported in 2 patients with type 2 diabetes mellitus in the dapagliflozin group and none in

the placebo group.

In a 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

Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.7% versus 3.5%, respectively; see **section 4.4**). 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 a study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 0.9% events versus 1.3% events, respectively.

In a reported study, the numbers of patients with serious adverse events of urinary tract infections were 0.6% in the dapagliflozin group and 0.7% in the placebo group. There were 0.2% patients with adverse events leading to discontinuations due to urinary tract infections in each of the dapagliflozin and placebo groups. In a reported study the numbers of patients with serious adverse events of urinary tract infections were 1.3% in the dapagliflozin group and 1.2% in the placebo group. There were 0.4% patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 0.3% in the placebo group.

In a reported study, the numbers of patients with serious adverse events of urinary tract infections were 1.3% in the dapagliflozin group and 0.8% in the placebo group. There were 0.4% patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 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 (0.9% versus 0.6% for serious adverse events, and 0.1% versus no 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 a safety pool study, 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 ≥ 60 mL/min/1.73 m²) 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 ≥ 30 and < 60 mL/min/1.73 m² (18.5% dapagliflozin 10 mg versus 9.3% placebo).

Further evaluation of patients who had renal-related adverse events reported that most had serum creatinine changes of ≤ 44 micromoles/L (≤ 0.5 mg/Dl) from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In a reported study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m²), 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 two reported studies, eGFR decreased over time in both the dapagliflozin group and the placebo group. In one reported study, the initial decrease in mean eGFR was -4.3 mL/min/1.73 m² in the dapagliflozin group and -1.1 mL/min/1.73 m² in the placebo group. At 20 months, change from baseline in eGFR was similar between the treatment groups: -5.3 mL/min/1.73 m² for dapagliflozin and -4.5 mL/min/1.73 m² for placebo. In another reported study, the decrease in mean eGFR at one month was -3.7 mL/min/1.73 m² in the dapagliflozin group and -0.4 mL/min/1.73 m² in the placebo group. At 24 months, change from baseline in eGFR was similar between treatment groups: -4.2 mL/min/1.73 m² in the dapagliflozin group and -3.2 mL/min/1.73 m² in the placebo group.

In a reported 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 m² in the dapagliflozin group and -0.8 mL/min/1.73 m² in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 m² in the dapagliflozin group and -8.6 mL/min/1.73 m² in the placebo group.

Paediatric population

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

Sitagliptin

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 %) (See **section 4.4**).

Tabulated list of adverse reactions

Adverse reactions are listed below (Table) 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 reported data).

Table: The frequency of adverse reactions reported from placebo-controlled clinical studies of sitagliptin monotherapy and post-marketing experience.

Adverse reaction	Frequency of adverse reaction
Blood and lymphatic system disorders	
thrombocytopenia	Rare
Immune system disorders	
hypersensitivity reactions including anaphylactic responses ^{*,†}	Frequency not known
Metabolism and nutrition disorders	
hypoglycaemia [†]	Common
Nervous system disorders	
headache	Common
dizziness	Uncommon
Respiratory, thoracic and mediastinal disorders	
interstitial lung disease [*]	Frequency not known
Gastrointestinal disorders	
constipation	Uncommon
vomiting [*]	Frequency not known
acute pancreatitis ^{*,†,‡}	Frequency not known
fatal and non-fatal haemorrhagic and necrotizing pancreatitis ^{*,†}	Frequency not known
Skin and subcutaneous tissue disorders	
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
Musculoskeletal and connective tissue disorders	
arthralgia*	Frequency not known
myalgia*	Frequency not known
back pain*	Frequency not known
arthropathy*	Frequency not known
Renal and urinary disorders	

impaired renal function*	Frequency not known
acute renal failure*	Frequency not known

* Adverse reactions were identified through post-marketing surveillance.

† See **section 4.4**.

‡ See reported TECOS Cardiovascular Safety Study below.

Description of selected adverse reactions for sitagliptin

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

Reported TECOS Cardiovascular Safety Study

The Trial Evaluating Cardiovascular Outcomes study was reported

with sitagliptin (TECOS) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m²), and 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 reported in patients receiving sitagliptin was similar to that in patients receiving placebo. In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.7 % in sitagliptin-treated patients and 2.5 % in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1.0 % in sitagliptin-treated patients and 0.7 % in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3 % in sitagliptin treated patients and 0.2 % in placebo-treated patients.

Metformin

In reported post marketing data and controlled clinical studies, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

The following adverse reactions may occur with metformin.

Frequencies are defined as follows: very common: $>1/10$; 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

Common

- Vitamin B12 decrease/deficiency (see **section 4.4**).

Very rare

- Lactic acidosis (see **section 4.4**).

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. 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, urticarial

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

Dapagliflozin

In healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose) no toxicity for dapagliflozin is reported. 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 reported 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 reported 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 haemo-dialysis has not been reported.

Sitagliptin

Minimal increases in QTc, not considered to be clinically relevant, were reported in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. No dose-related clinical adverse reactions have been reported 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 and approximately 13.5 % of the dose has been reported to be 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.

Metformin

Hypoglycaemia has not been reported with metformin doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose or concomitant risks of metformin 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 Pharmacodynamic properties

Pharmacotherapeutic group: Anti
Diabetics ATC code: A10BD15 and
A10BD07

Mechanism of action

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 diastolic function, and preserve renal function. The cardiac and renal benefits of dapagliflozin go beyond the blood glucose-lowering effect and are not limited to patients with diabetes as demonstrated in several clinical studies. Other effects include an increase in haematocrit and reduction in body weight.

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 reported 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 betacell) has been reported 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.

Pharmacodynamics effects

Increases in the amount of glucose excreted in the urine were reported in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose has been reported to be 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 reported 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 has been reported to increase 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 has been reported to range from -48.3 to -18.3 micromoles/L (-0.87 to -0.33 mg/dL).

Sitagliptin

Sitagliptin is a member of a class of oral anti-hyperglycaemic agents called dipeptidyl peptidase 4 (DPP-4) inhibitors. The improvement in glycaemic control reported with this medicinal product may be mediated by enhancing the levels of active incretin hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. Treatment with GLP-1 or with DPP-4 inhibitors in animal models of type 2 diabetes has been demonstrated to improve beta cell responsiveness to glucose and stimulate insulin biosynthesis and release. With higher insulin levels, tissue glucose uptake is enhanced. In addition, GLP-1 lowers glucagon secretion from pancreatic alpha cells. Decreased glucagon concentrations, along with higher insulin levels, lead to reduced hepatic glucose production, resulting in a decrease in blood glucose levels. The effects of

GLP-1 and GIP are glucose-dependent such that when blood glucose concentrations are low, stimulation of insulin release and suppression of glucagon secretion by GLP-1 are not reported. For both GLP-1 and GIP, stimulation of insulin release is enhanced as glucose rises above normal concentrations. Further, GLP-1 does not impair the normal glucagon response to hypoglycaemia. The activity of GLP-1 and GIP is limited by the DPP-4 enzyme, which rapidly hydrolyzes the incretin hormones to produce inactive products. Sitagliptin prevents the hydrolysis of incretin hormones by DPP-4, thereby increasing plasma concentrations of the active forms of GLP-1 and GIP. By enhancing active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in a glucose-dependent manner. In patients with type 2 diabetes with hyperglycaemia, these changes in insulin and glucagon levels lead to lower haemoglobin A1c (HbA1c) and lower fasting and postprandial glucose concentrations. The glucose dependent mechanism of sitagliptin is distinct from the mechanism of sulphonylureas, which increase insulin secretion even when glucose levels are low and can lead to hypoglycaemia in patients with type 2 diabetes and in normal subjects. 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.

In healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Metformin

Metformin is a biguanide with antihyperglycaemic effects, on both basal and postprandial hyperglycaemia. It does not stimulate insulin secretion and therefore does not cause hypoglycaemia.

Metformin reduces basal hyperinsulinemia, and in combination with insulin, reduces insulin requirement.

Metformin exerts its antihyperglycaemic effect via multiple mechanisms:

- Metformin reduces hepatic glucose production.
- Metformin facilitates peripheral glucose uptake and utilisation, in part by increasing insulin action.
- Metformin alters glucose turnover in the gut: Uptake from circulation is increased and absorption from food is decreased. Additional mechanisms attributed to the gut

include an increase in release of glucagon-like peptide 1 (GLP-1) and a decrease of bile acid resorption. Metformin alters the gut microbiome.

- Metformin can improve the lipid profile in hyperlipidaemic individuals.
- Use of metformin was associated with either a stable body weight or modest weight loss.
- Metformin is an adenosine monophosphate-protein-kinase (AMPK) activator and increases the transport capacity of all types of membrane glucose transporters (GLUTs).

5.2 Pharmacokinetic properties

Dapagliflozin

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) have been reported to be usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C_{max} and AUC_t values following once daily 10 mg doses of dapagliflozin have been reported to be 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is reported to be 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

Dapagliflozin is reported to be 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 has been reported to be 118 liters.

Biotransformation

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

The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin has been reported to be

12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously has been reported to be 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 [^{14}C]-dapagliflozin dose, 96% has been reported to be 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.

Special populations

Renal impairment

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 has been reported to be 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

In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of dapagliflozin have been reported to be up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences have not been reported to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin have been reported to be 40% and 67% higher than matched healthy controls, respectively.

Elderly (≥ 65 years)

There is no 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

Pharmacokinetics and pharmacodynamics (glucosuria) in children with type 2 diabetes mellitus aged 10-17 years have been reported to be similar to those reported in adults with type 2 diabetes mellitus.

Gender

The mean dapagliflozin AUC in females has been reported to be about 22% higher than in males.

Race

No clinically relevant differences in systemic exposures between White, Black or Asian races have been reported.

Body weight

Dapagliflozin exposure was reported 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.

Sitagliptin

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 µM•hr, C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since coadministration 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. Doseproportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution

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

Biotransformation

Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is reported to be excreted unchanged in the urine. Following a [¹⁴C] sitagliptin oral dose, approximately 16 % of the radioactivity has been reported to be excreted as metabolites of sitagliptin. Six metabolites were reportedly detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin.

The reported *in vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

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

Elimination

Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity has been reported to be 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 has been reported to be approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance has been reported to be 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 pglycoprotein 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 ($\text{IC}_{50}=160\text{ }\mu\text{M}$) or p-glycoprotein (up to $250\text{ }\mu\text{M}$) mediated transport at therapeutically relevant plasma concentrations. In a reported clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in patients

The pharmacokinetics of sitagliptin have been reported to be generally similar in healthy subjects and in patients with type 2 diabetes.

Renal impairment

Compared to normal healthy control subjects, plasma AUC of single dose 50 mg of sitagliptin has been reported to increase by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment ($\text{GFR} \geq 60$ to $< 90\text{ mL/min}$) and patients with moderate renal impairment ($\text{GFR} \geq 45$ to $< 60\text{ mL/min}$), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin has been reported to increase approximately 2-fold in patients with moderate renal impairment ($\text{GFR} \geq 30$ to $< 45\text{ mL/min}$), and approximately 4-fold in patients with severe renal impairment ($\text{GFR} < 30\text{ mL/min}$), including in patients with ESRD on haemodialysis. Sitagliptin was modestly

removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis session starting 4 hours postdose). 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.

Hepatic impairment

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

Elderly

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

Paediatric population

The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) have been reported 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. This is not considered to be a clinically meaningful difference compared to adult patients based on the flat PK/PD relationship between the dose of 50 mg and 100 mg. No studies with sitagliptin have been reported in paediatric patients with age <10 years.

Other patient characteristics

No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a 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 the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a T_{max} at 7 hours (T_{max} for the immediate release tablet is 2.5 hours).

At steady state, similar to the immediate release formulation, C_{max} and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000mg of metformin prolonged release tablets is similar to that reported after administration of 1000mg of metformin immediate release tablets b.i.d.

Intrasubject variability of C_{max} and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.

When the prolonged release tablet is administered in fasting conditions the AUC is decreased by 30% (both C_{max} and T_{max} are unaffected).

Mean metformin absorption from the prolonged release formulation is almost not altered by meal composition.

No accumulation is observed after repeated administration of up to 2000mg of metformin as prolonged release tablets.

Following a single oral administration of 1500 mg of metformin prolonged release 750 mg, a mean peak plasma concentration of 1193 ng/ml is achieved with a median value of 5 hours and a range of 4 to 12 hours.

Metformin prolonged release 750 mg was shown to be bioequivalent to metformin prolonged release 500 mg at a 1500 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

Following a single oral administration in the fed state of one tablet of metformin prolonged release 1000 mg, a mean peak plasma concentration of 1214 ng/ml is achieved with a median time of 5 hours (range of 4 to 10 hours).

Metformin prolonged release 1000 mg was reported to be bioequivalent to metformin prolonged release 500 mg at a 1000 mg dose with respect to C_{max} and AUC in healthy fed and fasted subjects.

When the 1000 mg prolonged release tablet is administered in fed conditions the AUC is increased by 77% (C_{max} is increased by 26% and T_{max} is slightly prolonged by about 1 hour).

Distribution

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

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 groups of patients

Renal impairment

The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see **section 4.2**).

5.3 Preclinical safety data

Dapagliflozin

The 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 ≥ 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 reported in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate reported 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 reported to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was reported 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 reported only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 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 studies of embryo-foetal development reported 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 reported 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.

Sitagliptin

Renal and liver toxicity were reported in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was reported at 19 times the human exposure level. Incisor teeth abnormalities were reported 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 reported in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also reported histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was reported at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in reported 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 adverse effects upon fertility were reported in male and female rats given sitagliptin prior to and throughout mating. In a reported pre-/postnatal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies reported 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 reported in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these reported findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

Metformin

The reported preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Anhydrous lactose
Crospovidone
Colloidal silicon dioxide
Dibasic calcium phosphate
Anhydrous lactose
Ferric oxide
Sodium stearyl fumarate.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store up to 30°C. Protected from moisture.

6.5 Nature and contents of the container

DAPEFY SM packed in 4x7's in Cold form blister pack

6.6 Special precautions for disposal <and other handling>

None

**7. MARKETING AUTHORIZATION HOLDER AND
MANUFACTURING SITE ADDRESSES**

Marketing Authorization Holder

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Sun House, 201 B/1,
Western Express
Highway, Gurgaon
(East), Mumbai,
400063, India

Manufacturing site addresses

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Palashbari, District - Kamrup, Guwahati, Assam – 781128

8. MARKETING AUTHORISATION NUMBER

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10. DATE OF REVISION OF THE TEXT

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