PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DAPAGLIFLOZIN 5 SANDOZ (Film-coated tablets)

DAPAGLIFLOZIN 10 SANDOZ (Film-coated tablets)

DAPAGLIFLOZIN SANDOZ IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES MELLITUS (see section 4.3). DAPAGLIFLOZIN SANDOZ IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES AND NOT INDICATED FOR THE TREATMENT OF ANY OTHER CONDITIONS EXCEPT FOR THE TREATMENT OF TYPE 2 DIABETES AND HEART FAILURE.

There have been reports of metabolic acidosis, including ketoacidosis, which were serious life-threatening or fatal, in patients taking DAPAGLIFLOZIN SANDOZ.

Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even If blood glucose levels are below 14 mmol/L. DAPAGLIFLOZIN SANDOZ should be discontinued and the patient should be promptly evaluated and managed accordingly.

Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with DAPAGLIFLOZIN SANDOZ.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery.

DAPAGLIFLOZIN SANDOZ is contraindicated in these patients (see section 4.3).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of DAPAGLIFLOZIN 5 SANDOZ contains 5 mg of dapagliflozin.

Each film-coated tablet of DAPAGLIFLOZIN 10 SANDOZ contains 10 mg of dapagliflozin.

Excipients with known effect:

Contains Sugar

Each film-coated tablet of DAPAGLIFLOZIN 5 SANDOZ contains 81,00 mg lactose.

Each film-coated tablet of DAPAGLIFLOZIN 10 SANDOZ contains 162,00 mg lactose.

For full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

DAPAGLIFLOZIN 5 SANDOZ mg (Film-coated tablets)

Light yellow, round, biconvex film coated tablet debossed with “DN 5” on one side.

DAPAGLIFLOZIN 10 SANDOZ mg (Film-coated tablets)

Light yellow, oval, biconvex film coated tablet debossed with “DN 10” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 diabetes mellitus:

DAPAGLIFLOZIN SANDOZ is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- as monotherapy as an adjunct to diet and exercise to improve glycaemic control.
- as add-on combination therapy, with glucose-lowering medicines, including metformin, a thiazolidinedione, a sulfonylurea, a DPP4 inhibitor, or insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
- to reduce the risk of developing new or worsening existing heart failure or cardiovascular death in patients with established cardiovascular (CV) disease or multiple CV risk factors.

Heart failure:

DAPAGLIFLOZIN SANDOZ is indicated in adults to reduce the risk of worsening heart failure or cardiovascular death, in patients with heart failure (NYHA class II-IV), and with a left ventricular ejection fraction (LVEF) ≤ 40 %.

4.2 Posology and method of administration

Posology:

Type 2 diabetes mellitus:

Monotherapy and add-on combination therapy:

The recommended dose is 10 mg DAPAGLIFLOZIN SANDOZ once daily for monotherapy and add-on combination therapy with other glucose-lowering medicines, including metformin, a thiazolidinedione, a sulfonylurea, a DPP4 inhibitor, or insulin.

The recommended starting doses of DAPAGLIFLOZIN SANDOZ and metformin when used as initial combination therapy are 10 mg DAPAGLIFLOZIN SANDOZ plus 500 mg metformin once daily. Patients with inadequate glycaemic control on this starting dose should have their metformin dose increased according to approved metformin Professional Information.

Use with medicines known to cause hypoglycaemia:

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

Heart failure:

The recommended dose of DAPAGLIFLOZIN SANDOZ is 10 mg taken orally once daily at any time of the day regardless of meals. DAPAGLIFLOZIN SANDOZ can be used in conjunction with other heart failure therapies.

Special Populations:

Renal impairment:

No dosage adjustment is required based on renal function.

In patients with diabetes mellitus, the glucose lowering efficacy of DAPAGLIFLOZIN SANDOZ is reduced in patients with eGFR < 45 mL/min/1,73 m^2 (see sections 4.4). Therefore, if eGFR falls below 45 mL/min/1,73 m^2, additional glucose lowering treatment should be considered in patients with type 2 diabetes mellitus if further glycaemic control is needed. Treatment with dapagliflozin should be continued for the management of renal and cardiovascular comorbidities.

Hepatic impairment:

No dosage adjustment for DAPAGLIFLOZIN SANDOZ is necessary for patients with mild (CHILD-PUGH class A) or moderate (CHILD-PUGH class A) hepatic impairment. DAPAGLIFLOZIN SANDOZ is not recommended for patients with severe (CHILD-PUGH class C) hepatic impairment as efficacy has not been established (see section 5.2).

Patients at risk for volume depletion:

For patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics, a 5 mg starting dose of DAPAGLIFLOZIN SANDOZ may be appropriate (see section 4.4).

Elderly:

No dosage adjustment for DAPAGLIFLOZIN SANDOZ is required based on age (see section 4.4).

Paediatric population:

Safety and effectiveness of DAPAGLIFLOZIN SANDOZ in paediatric and adolescent patients have not been established.

Method of administration:

For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance (dapagliflozin) or to any of the excipients listed in section 6.1.
- Moderate and severe renal impairment with GFR < 45 mL/min/1,73 m^2, end stage renal failure or patients on dialysis when used for type 2 diabetes mellitus indication.
- Diabetes mellitus Type 1.

- Pregnant women or women who are breastfeeding their infants (see section 4.6).
- Patients with history of pancreatitis or pancreatic surgery (see 4.4)

4.4 Special warnings and precautions for use

General:

DAPAGLIFLOZIN SANDOZ may cause a decrease in systolic blood pressure and diastolic blood pressure. DAPAGLIFLOZIN SANDOZ should not be used for the treatment of diabetic ketoacidosis.

Metabolic acidosis including ketoacidosis in patients with diabetes mellitus:

There have been reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 2 diabetes mellitus taking DAPAGLIFLOZIN SANDOZ. DAPAGLIFLOZIN SANDOZ is contraindicated for the treatment of patients with type1 diabetes mellitus (see section 4.3).

Patients treated with DAPAGLIFLOZIN SANDOZ who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, DAPAGLIFLOZIN SANDOZ should be discontinued, and the patient should be promptly evaluated.

Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. DAPAGLIFLOZIN SANDOZ is not indicated in these patients (see section 4.3).

Renal impairment:

There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1,73 m^2.

DAPAGLIFLOZIN SANDOZ is not recommended for the treatment of type 2 diabetes mellitus to improve glycaemic control when eGFR is persistently below 45 mL/min/1,73 m^2 as the glycaemic efficacy of dapagliflozin is dependent on renal function (see section 4.2). However, treatment with DAPAGLIFLOZIN SANDOZ should be continued for the management cardiovascular comorbidities and additional glucose lowering treatment should be considered if further glycaemic control is needed.

Monitoring of renal function is recommended as follows:

- Prior to initiation of DAPAGLIFLOZIN SANDOZ and at least annually thereafter.
- Prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.
- For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below eGFR < 45 mL/min/1,73 m^2, DAPAGLIFLOZIN SANDOZ treatment should be discontinued (See sections 4.3).

Hepatic impairment:

There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment (see sections 4.2 and 5.2).

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

Dapagliflozin may cause a decrease in systolic and diastolic blood pressure. Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1). 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. A 5 mg starting dose of DAPAGLIFLOZIN SANDOZ may be appropriate in these patients (see section 4.2).

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. DAPAGLIFLOZIN SANDOZ should be permanently discontinued in patients who develop volume depletion (see section 4.8).

Diabetic ketoacidosis:

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. If ketoacidosis is suspected, DAPAGLIFLOZIN SANDOZ should be discontinued and the patient should be promptly evaluated.

In patients where DKA is suspected or diagnosed, DAPAGLIFLOZIN SANDOZ 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 SANDOZ, 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 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. DAPAGLIFLOZIN SANDOZ is contraindicated in patients with type 1 diabetes (see section 4.3).

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 SANDOZ should not be used for treatment of patients with type 1 diabetes.

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 4.8). 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 SANDOZ 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 SANDOZ should be considered when treating pyelonephritis or urosepsis.

SGLT2 inhibitors such as DAPAGLIFLOZIN SANDOZ have been associated with an increased risk of urinary tract infection and/or genital infection in both males and females caused by bacteria and/or fungi. Genital and fungal infections appear to be more common in females. Balanoposthitis in males may result in phimosis. Temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis. Discontinuation of dapagliflozin may be considered in cases of recurrent urinary tract infections, see section 4.8 Undesirable effects. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Use with medicines known to cause hypoglycaemia:

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 SANDOZ (see section 4.8).

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 medicines 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 4.2, and 5.2).

Cardiac failure:

Experience with dapagliflozin in New York Heart Association (NYHA) class IV is limited.

Paediatric use:

Safety and efficacy of DAPAGLIFLOZIN SANDOZ in paediatric patients has not been established.

Lower limb amputations:

An increased 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.

Other populations:

Patients with severe renal impairment (eGFR < 20 mL/min/1.73m^2) or End Stage Renal Disease or with recent (< 2 months) cardiovascular event or who are breast-feeding or are pregnant, have been excluded from clinical studies.

Urine laboratory assessments:

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

Lactose:

DAPAGLIFLOZIN SANDOZ contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance total lactose deficiency or glucose-galactose malabsorption should not take DAPAGLIFLOZIN SANDOZ.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions:

Diuretics:

DAPAGLIFLOZIN SANDOZ may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

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 sections 4.2 and 4.8).

Pharmacokinetic interactions:

The metabolism of dapagliflozin is primary via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9). The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide 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 medicines that are metabolized by these enzymes. Dapagliflozin is a weak substrate of the P- glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters.

The dependence of dapagliflozin elimination on dapagliflozin 3-O- glucuronide formation in humans also suggests the possibility of interactions mediated by UGT1A9. Ketoconazole is an *in vitro* inhibitor of dapagliflozin 3-O-glucuronide formation by UGT1A9 (IC50 = 32 µM).

Effects of other medicines on DAPAGLIFLOZIN SANDOZ:

Interaction studies conducted in healthy participants, using mainly a single-dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin (a human OCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a human OAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose (an alpha-glucosidase inhibitor), hydrochlorothiazide, bumetanide, valsartan, or simvastatin (a CYP3A4 substrate). Therefore, meaningful interaction of dapagliflozin with other substrates of hOCT-1, hOCT-2, hOAT-3, P-gp, CYP2C8, CYP2C9, CYP3A4, and other alpha-glucosidase inhibitor would not be expected.

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.

Co-administration of dapagliflozin and bumetanide did not meaningfully change the pharmacodynamic effect of dapagliflozin to increase urinary glucose excretion in healthy participants.

Effect of DAPAGLIFLOZIN SANDOZ on other medicines:

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.

In interaction studies conducted in healthy participants, using mainly single dose design, dapagliflozin did not alter the pharmacokinetics of metformin (an hOCT 1 and hOCT 2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (a hOAT 3 substrate and P- glycoprotein substrate), glimepiride (a CYP2C9 substrate), hydrochlorothiazide, bumetanide,

valsartan, simvastatin (a CYP3A4 substrate), digoxin (a P-gp substrate) or warfarin (S warfarin, a CYP2C19 substrate, R warfarin or the anticoagulatory effects of warfarin as measured by the prothrombin time [International Normalised Ratio (INR)]). Therefore, dapagliflozin is not a clinically meaningful inhibitor of hOCT-1, hOCT-2, hOAT-3, P-gp transporter pathway, and CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mediated metabolism.
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.

Co-administration of dapagliflozin and bumetanide did not meaningfully alter the steady state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy participants.
Dapagliflozin did not affect the anticoagulant activity of warfarin, as measured by the prothrombin time (International Normalized Ratio [INR]).

Other interactions:

The effect of smoking, diet, herbal products and alcohol use on the pharmacokinetics of dapagliflozin have not been studied.

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 of monitor glycaemic control is advised.

4.6 Fertility, pregnancy and lactation

Pregnancy:

DAPAGLIFLOZIN SANDOZ is contraindicated in pregnancy (see section 4,3). Maternal exposure to DAPAGLIFLOZIN SANDOZ in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. When pregnancy is detected, treatment with DAPAGLIFLOZIN SANDOZ should be discontinued.

Breastfeeding:

Mothers on DAPAGLIFLOZIN SANDOZ should not breast-feed their infants. It is unknown whether DAPAGLIFLOZIN SANDOZ is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk.
DAPAGLIFLOZIN SANDOZ should not be used while breastfeeding and exposure to DAPAGLIFLOZIN SANDOZ should be avoided during the first 2 years of life (see section 4. 3).

Fertility:

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

4.7 Effects on ability to drive and use machines

DAPAGLIFLOZIN SANDOZ causes dizziness and may have an influence on the ability to drive and use machines. Patients should also be alerted to the risk of hypoglycaemia when DAPAGLIFLOZIN SANDOZ is used in combination with a sulphonylurea or insulin. Patients should therefore be warned to be cautious when driving a vehicle or operating machinery.

4.8 Undesirable effects

System organ class	Frequent	Less Frequent

Infections and infestations	Vulvovaginitis, balanitis and related genital infections, urinary tract infection, including pyelonephritis, cystitis	Fungal infection, necrotising fasciitis of the perineum (Fournier's gangrene)
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylureas (SU) or insulin)	Volume depletion, dehydration, hypovolaemia, hypotension, thirst, diabetic ketoacidosis (when used in type 2 diabetes mellitus)
Nervous system disorders	Dizziness	
Gastro-intestinal disorders		Constipation, dry mouth
Skin and sub-cutaneous tissue disorders	Rash	Hyperhidrosis, angioedema
Musculo-skeletal and connective tissue disorders	Back pain	
Renal and urinary disorders	Glucosuria, dysuria, polyuria	Nocturia, tubulointerstitial nephritis
Reproductive systems and breast disorders		Vulvovaginal pruritus, pruritus genital

Investigations	Dyslipidaemia, haematocrit increased, creatinine renal clearance decreased during initial treatment	Blood urea increased, blood creatinine increased during initial treatment, weight decreased

Post-marketing adverse events:

Spontaneous reports:

Skin and sub-cutaneous tissue disorders: Rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, rash erythematous.

Phimosis have been reported with the use of SGLT2 inhibitors such as DAPAGLIFLOZIN SANDOZ.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of DAPAGLIFLOZIN SANDOZ is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via the website: https://pvi1j.solutions.iqvia.com or the e-mail address, adverse.event.sac@sandoz.com.

4.9 Overdose

Symptoms of overdose:

In overdose, side effects may be elicited or exacerbated (see section 4.8). Studies indicate that dapagliflozin did not show any toxicity in healthy participants at single oral doses up to 500 mg (50 times the maximum recommended human dose).

Treatment of overdose:

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.2 Oral hypoglycaemics

Pharmacotherapeutic group: Sodium-glucose co-transporter 2 (SGLT2) inhibitors

ATC code: A10BK01.

Mechanism of action:

Dapagliflozin is a reversible inhibitor of sodium glucose co- transporter 2 (SGLT2) that improves glycaemic control in patients with type 2 diabetes mellitus and provides cardiac benefits. 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 is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure. Secondary effects of SGLT2 inhibition with dapagliflozin also include a modest reduction in blood pressure, reduction in body weight, and an increase in haematocrit. The cardiac benefits of dapagliflozin are not solely dependent on the blood glucose lowering effect. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid may be mechanisms underlying the cardio- renal beneficial effects of dapagliflozin.

Dapagliflozin reduces 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 glomerular filtration rate (GFR). Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging.

SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 3 000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamic effects:

The urinary glucose excretion with dapagliflozin results in osmotic diuresis and increases in urinary volume. The increase in urinary volume may be associated with a transient increase in urinary sodium excretion that which may not be associated with changes in serum sodium concentrations. Dapagliflozin may cause a decrease in systolic blood pressure and diastolic blood pressure. Urinary uric acid excretion was also increased and accompanied by a reduction in serum uric acid concentration. At 24 weeks, changes in serum uric acid concentrations from baseline ranged from -0,0183 mmol/L to -0,0483 mmol/L.

5.2 Pharmacokinetic properties

Absorption:

Dapagliflozin was absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78 %. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy participants. 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 SANDOZ can be administered with or without food.

Distribution:

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 litres.

Biotransformation:

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. 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 participants. Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61 % of a 50 mg [14C]- dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42 % [based on $AUC_{(0-12\ h)}$] of total plasma

radioactivity, similar to the 39 % contribution by parent compound. No other metabolite accounted for > 5 % of the total plasma radioactivity at any time point measured. 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:

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2 % as unchanged dapagliflozin. After administration of 50 mg [14C]-dapagliflozin dose, 96 % was recovered, 75 % in urine and 21 % in faeces. In faeces, approximately 15 % of the dose was excreted as parent compound.

Special populations:

Renal impairment:

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin that were 32 %, 60 % and 87 % higher, respectively, than those of patients with type 2 diabetes mellitus and normal renal function. At dapagliflozin 20 mg once daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or 24-hour glucose excretion. The renal glucose clearance and 24-hour glucose excretion were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. 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 patients with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between

renal impairment groups or compared to healthy participants. The impact of haemodialysis on dapagliflozin exposure is not known. Dapagliflozin is contraindicated in patients whose GFR is less than 45 mL/min/1,73 m^2 (see section 4.3).

Hepatic impairment:

A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy participants. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12 % and 36 % higher, respectively, compared to healthy matched control participants. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40 % and 67 % higher than matched healthy controls, respectively. Dapagliflozin is not recommended for use in severe hepatic impairment (see section 4.4).

Age:

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The effect of age (young: ≥ 18 to < 40 years [n = 105] and elderly: ≥ 65 years [n = 224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥ 40 to < 65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10,4 % lower than in the reference group [90 % CI: 87,9; 92,2 %] and 25 % higher in elderly patients compared

to the reference group [90 % CI: 123;129 %]. These differences in systemic exposure were considered not to be clinically meaningful.

Paediatric and adolescent:

Pharmacokinetics in the paediatric and adolescent population have not been studied.

Body Weight:

In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high body weight participants (≥ 120 kg, n = 91) were estimated to be 78,3% [90 % CI:78,2; 83,2 %] of those of reference participants with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥ 120 kg) is recommended. Participants with low body weights (< 50 kg) were not well represented in the healthy participants and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of participants. The simulated mean dapagliflozin systemic exposures in low body weight participants were estimated to be 29 % higher than participants with the reference group body weight. This difference is considered to be small and, based on these findings, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (< 50 kg) is recommended.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Table core:

Hypromellose 2910, 3 mPas

Lactose Monohydrate

Microcrystalline Cellulose

Croscarmellose Sodium

Magnesium stearate

Film coating:

Hypromellose 2910, 6 mPas

Hydroxypropyl Cellulose

Triethyl Citrate

Titanium Dioxide

Ferric Oxide Yellow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

Do not store above 25 °C.

6.4 Special precautions for storage

This medicine does not require any special storage conditions

6.5 Nature and contents of container

DAPAGLIFLOZIN SANDOZ film-coated tablets 5 and 10 mg are packed into an aluminium/aluminium foil blister pack.

The blisters are packed together with the leaflet into the cardboard carton.

Pack sizes:

The available pack sizes are 30's and 100's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBERS

DAPAGLIFLOZIN 5 SANDOZ: 58/21.2/0107.105

DAPAGLIFLOZIN 10 SANDOZ: 58/21.2/0108.106

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 January 2026

10. DATE OF REVISION OF THE TEXT

Not applicable.

[1]Company Reg. No.: 1990/001979/07