SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

TAPLEO® 5 (Tablet)

TAPLEO® 10 (Tablet)

TAPLEO IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. TAPLEO IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES.

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

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 11 mmol/L. TAPLEO 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 TAPLEO.
Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. TAPLEO is contraindicated in these patients.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAPLEO 5:

Each tablet contains the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol.

Contains sugar: 25 mg lactose anhydrous per 5 mg tablet

TAPLEO 10:

Each tablet contains the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol.

Contains sugar: 50 mg lactose anhydrous per 10 mg tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

TAPLEO 5:

Tablets

Yellow, biconvex, 0.7 cm diameter round, film-coated tablet with "5” debossed on one side and "1427" debossed on the other side.

TAPLEO 10:

Tablets

Yellow, biconvex, approximately 1.1 x 0.8 cm diamond shaped, film-coated tablet with "10” debossed on one side and "1428" debossed on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 diabetes mellitus

TAPLEO 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

TAPLEO 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

Type 2 diabetes mellitus

Monotherapy and add-on combination therapy

The recommended dose is 10 mg TAPLEO 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.

Use with medicines known to cause hypoglycaemia:

When TAPLEO 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 TAPLEO is 10 mg taken orally once daily at any time of the day regardless of meals. TAPLEO can be used in conjunction with other heart failure therapies.

Special Populations

Renal impairment:

Treatment of diabetes mellitus

No dosage adjustment is required based on renal function.

As glycaemic efficacy is dependent on renal function (see sections 4.4 and 4.8), TAPLEO is not recommended to improve glycaemic control in the treatment of diabetes in patients where eGFR is below 45 mL/min/1,73 m^{2}.

Monitoring of renal function is recommended as follows:

- Prior to initiation of TAPLEO 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, TAPLEO treatment should be discontinued (See sections 4.3).

Treatment of heart failure

No dosage adjustment is required based on renal function.

Hepatic impairment:

No dosage adjustment for TAPLEO is necessary for patients with mild or moderate hepatic impairment. TAPLEO is not recommended for patients with severe hepatic impairment as efficacy has not been established. (See section 5.2).

Elderly:

No dosage adjustment for TAPLEO is required based on age. (See section 4.4).

Paediatric population:

Safety and effectiveness of TAPLEO in paediatric and adolescent patients have not been established. No data is available.

4.3 Contraindications

- Hypersensitivity to dapaglifozin or to any of the excipients of TAPLEO.
- 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 breast-feeding their infants (See section 4.6).

4.4 Special warnings and precautions for use

General:

TAPLEO may cause a decrease in systolic blood pressure and diastolic blood pressure.

TAPLEO 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 TAPLEO. TAPLEO is contraindicated for the treatment of patients with type 1 diabetes mellitus (see section 4.3)

Patients treated with TAPLEO 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 11 mmol/L (196 mg/dL). If ketoacidosis is suspected, TAPLEO 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. TAPLEO is not indicated in these patients.

Impairment of renal function/acute kidney injury:

SGLT2 inhibitors such as TAPLEO may cause a decrease in the glomerular filtration rate (GFR), with an increase in serum creatinine and serum urea. Acute kidney injury (AKI) has been reported with the use of SGLT2 inhibitors.

Based on their mode of action, SGLT2 inhibitors may cause glycosuria, osmotic diuresis, fluid and electrolyte loss with a risk of dehydration/hypovolaemia and hypotension, which may precipitate acute kidney injury. Renal function and hydration status should be assessed before treatment is initiated with a SGLT2 inhibitor such as TAPLEO and should be frequently monitored during treatment.

Other factors that may predispose patients to AKI during treatment with SGLT2 inhibitors include reduced oral intake of fluids, congestive cardiac failure, gastrointestinal fluid losses, excessive heat exposure, and concomitant use of medicines such as diuretics, NSAIDS, ACE inhibitors and ARBs. Discontinue treatment with SGLT2 inhibitors in patients with AKI and consider other appropriate treatment options for their diabetes mellitus.

SGLT2 inhibitors such as TAPLEO, are contraindicated in patients with moderate to severe renal impairment and in patients on dialysis (See section 4.3).

There is limited experience with TAPLEO in patients with severe renal impairment (eGFR < 30 mL/min/1,73 m^2) or end-stage renal disease (ESRD).

Urinary tract and genital infections:

SGLT2 inhibitors such as TAPLEO 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.

Treatment of diabetes mellitus

TAPLEO is not recommended for use in the treatment of diabetes to improve glycaemic control when eGFR is below 45 mL/min/1,73 m^2 as the glycaemic efficacy of dapagliflozin is dependent on renal function. Renal function should be evaluated prior to initiation of TAPLEO and periodically thereafter (See section 4.2).

Use with medicines known to cause hypoglycaemia:

Insulin and insulin secretagogues, such as sulfonylureas, 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 TAPLEO (See section 4.8).

Paediatric use:

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

Other populations:

Patients with severe renal impairment (eGFR < 30 mL/min/ 1,73 m^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.

Lactose:

TAPLEO contains lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency, or glucose-galactose malabsorption should not use TAPLEO.

4.5 Interaction with other medicines, and other forms of interaction

The metabolism of dapagliflozin is primarily mediated by UGT1A9- dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In in-vitro studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. 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 TAPLEO:

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics of TAPLEO were 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.

A 22 % decrease in dapagliflozin systemic exposure following co-administration with rifampicin was considered not to be large enough to warrant a dose adjustment.

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

Effect of TAPLEO on other medicines:

In interaction studies conducted in healthy subjects, using mainly single dose design, TAPLEO 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.

Co-administration of dapagliflozin and bumetanide did not meaningfully alter the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

Dapagliflozin did not affect the anticoagulant activity of warfarin, as measured by the prothrombin time (International Normalized Ratio [INR]).

Other interactions:

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

Interference with 1,5-anhydroglucitol (1,5-AG) Assay:

Monitoring glycaemic control with 1,5-AG assay should not be used, as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors, including TAPLEO. Alternative methods of monitoring glycaemic control should be used.

4.6 Fertility, pregnancy and lactation

Pregnancy:

TAPLEO is contraindicated in pregnancy.

Maternal exposure to TAPLEO in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. When pregnancy is detected, TAPLEO should be discontinued (See section 4.3)

Breastfeeding:

Mothers on TAPLEO should not breast-feed their infants.

Alternatively, mothers breastfeeding their infants must not use TAPLEO. Studies in rats have shown excretion of TAPLEO in milk. Exposure to TAPLEO must be avoided during the first 2 years of life (See section 4.3).

Fertility:

The effect of dapagliflozin on fertility in humans has not been studied.

4.7 Effects on ability to drive and use machines

Patients must bear in mind the possibility of hypoglycaemia and its effects on their motor skills.

4.8 Undesirable effects

a. Summary of the safety profile

More than 28 000 patients with type 2 diabetes and heart failure were randomised, including 15 000 patients treated for type 2 diabetes and more than 2 000 subjects treated for heart failure with TAPLEO, in 22 double-blind, controlled, clinical safety and efficacy studies conducted to evaluate the effects of TAPLEO. TAPLEO 10 mg was evaluated in 13 of these studies.

The incidence of adverse reactions was determined using a pre- specified pool of patients from 13 short-term (mean duration 22 weeks), placebo-controlled studies in type 2 diabetes. Across these 13 studies, 2 360 patients were treated once daily with TAPLEO 10 mg and 2 295 were treated with placebo (either as monotherapy or in combination with other antidiabetic therapies).

Additionally, TAPLEO 5 mg was evaluated in a 12-study, short-term, placebo-controlled pool of type 2 diabetes patients that included 1 145 patients treated with TAPLEO 5 mg (mean exposure = 22 weeks) and 1 393 patients treated with placebo (mean exposure = 21 weeks), either as monotherapy or in combination with other antidiabetic therapies. In the dedicated cardiovascular (CV) outcomes study in patients with type 2 diabetes mellitus (DECLARE), 8 574 patients received TAPLEO 10 mg and 8 569 received placebo for a median exposure time of 48 months. In total, there were 30 623 patient-years of exposure to TAPLEO. In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF), 2 368 patients were treated with dapagliflozin 10 mg and 2 368 patients with placebo for a median exposure time of 18 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥30 mL/min/m^2.

The safety profile of dapagliflozin was overall consistent across the studied indications. DKA was observed only in patients with diabetes mellitus.

The adverse reactions are listed by system organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, <1/100) and rare (≥ 1/10 000, < 1/1 000).

b) Tabulated list of adverse reactions

Table 1 Adverse reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Studies[a] reported in ≥ 2 % of patients treated with TAPLEO 10 mg and ≥ 1 % more frequently than in patients treated with placebo.

System organ class	**Very common**	**Common***	**Uncommon****	**Rare**
Infections and infestations		Vulvo-vaginitis, balanitis and related genital infections[b,c] Urinary tract infection[b,e], including pyelo-nephritis, cystitis.		
Metabolism and nutrition disorders	Hypo-glycaemia (when used with SU or insulin)[b]		Volume depletion, dehydration, hypovolaemia, hypotension Thirst**	Diabetic ketoacid-osis[b]
Gastro-intestinal disorders			Constipation	
Skin and sub-cutaneous tissue disorders		Rash[h]	Hyperhidrosis	

Musculo-skeletal and connective tissue disorders		Back pain		
Renal and urinary disorders	Glucosuria	Dysuria Polyuria[d]	Nocturia	
Investigations		Dyslipid-aemia[f] Haematocrit increased[g]	Blood urea increased	
Reproductive systems and breast disorders			Vulvovaginal pruritus	

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

[b] See corresponding subsection below for additional information.

[c] Genital infection includes the preferred terms: 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, balanoposthitis, genitourinary tract infection, penile abscess, posthitis.

[d] Polyuria includes the preferred terms: pollakiuria, polyuria, increased urine output, osmotic diuresis.

[e] Urinary tract infection includes the preferred terms: Escherichia urinary tract infection, genitourinary tract infection, trigonitis, urethritis, kidney infection, and prostatitis.

[f] 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 %.

[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] Adverse reaction was identified through post-marketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N = 5 936, all control, N = 3 403), the frequency of rash was similar for dapagliflozin (1,4 %) and all control (1,4 %), respectively (see “Post-marketing adverse events”).

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

** Reported by the investigator 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 dapagliflozin10 mg compared to placebo.

c. Description of selected adverse reactions

Genital infections:

Events of genital infections were reported in 5,5 % and 0,6 % of patients who received TAPLEO 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. Infections were more frequently reported in females (8,4 % TAPLEO 10 mg vs. 1,2% placebo) than in males (3,4 % TAPLEO 10 mg vs. 0,2 % placebo).

In the DECLARE study, the number of patients with SAEs of genital infections were few and balanced: 2 (< 0,1 %) patients in each of the TAPLEO and placebo groups.

In the DAPA-HF study, no patient reported a SAE of genital infections in the TAPLEO group and one in the placebo group. There were 7 (0,3 %) patients with adverse events leading to discontinuations (DAE) due to genital infections in the TAPLEO group and none in the placebo group.

Urinary tract infections:

Events of urinary tract infections were reported in 4,7 % and 3,5 % of patients who received TAPLEO 10 mg and placebo, respectively, in the short term, placebo-controlled pool. Infections were more frequently reported in females (8,5 % TAPLEO 10 mg vs. 6,7 % placebo) than in males (1,8 % TAPLEO 10 mg vs. 1,3 % placebo).

In the DECLARE study there were fewer patients with SAEs of urinary tract infections in the TAPLEO group compared with the placebo group: 79 (0,9 %) and 109 (1,3 %), respectively.

In the DAPA-HF study, the number of patients with SAEs of UTI were low and balanced: 14 (0,6 %) patients in the TAPLEO group and 17 (0,7 %) patients in the placebo group. There were 5 (0,2 %) patients with DAEs due to urinary tract infections in each of the TAPLEO and placebo groups.

Diabetic ketoacidosis (DKA):

In the DECLARE CV outcomes study with a median exposure time of 48 months, events of DKA were reported in 27 patients in the TAPLEO 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the TAPLEO group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see section 4.4).

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

Hypoglycaemia:

The frequency of hypoglycaemia depended on the type of background therapy used in each study. Studies with add-on sulfonylurea and add-on insulin therapies had higher rates of hypoglycaemia. (See section 4.4). In an add-on to glimepiride study up to 24 weeks, episodes of hypoglycaemia were reported in 10 (6,6 %) patients in the TAPLEO 10 mg plus glimepiride group and 3 (2,1 %) patients in the placebo plus glimepiride group.

In an add-on to insulin study up to 24 weeks, episodes of hypoglycaemia were reported in 79 (40,3 %) patients in the TAPLEO 10 mg plus insulin group and in 67 (34 %) patients in placebo plus insulin group. Patients in this study could also be treated with a maximum of 2 oral anti-diabetes medications (OADs) including metformin.

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

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

Laboratory findings:

Haematocrit:

A moderate increase in haematocrit occurs and may be an indication of volume depletion.

Serum inorganic phosphorous:

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in TAPLEO 10 mg treated patients compared with placebo (mean increases of 0,0419 mmol/L vs. 0,0129 mmol/L, respectively). Similar results were seen at Week 102. Higher proportions of patients

with marked laboratory abnormalities of hyperphosphatemia (≥ 1,81 mmol/L if age 17-65 or ≥ 1,65 mmol/L if ≥ age 66) were reported in TAPLEO 10 mg group vs. placebo at Week 24 (1,7 % vs. 0,9 %, respectively) and during the short-term plus long-term phase (3,0 % vs. 1,6 %, respectively). The clinical relevance of these findings is unknown.

Lipids:

In the pool of 13 placebo-controlled studies, small changes from baseline in mean lipid values were reported at Week 24 in TAPLEO 10 mg treated patients compared with placebo. Mean percent change from baseline at Week 24 for TAPLEO 10 mg vs. placebo, respectively was as follows: total cholesterol 2,5 % vs. 0,0 %; HDL cholesterol 6,0 % vs. 2,7 %; LDL cholesterol 2,9 % vs. -1,0 %; triglycerides -2,7 % vs. -0,7 %. Mean percent change from baseline at Week 102 for TAPLEO 10 mg vs. placebo, respectively was as HDL cholesterol 6,6 % vs. 2,1 %; LDL cholesterol 2,9 % vs. -2,2 %; follows: total cholesterol 2,1 % vs. -1,5 %; triglycerides -1,8 % vs. -1,8 %. The ratio between LDL cholesterol and HDL cholesterol decreased for all treatment groups at Week 24.

In the CV outcomes study, no clinical important differences in total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides were seen.

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.

Acute kidney injury (AKI) and phimosis have been reported with the use of SGLT2 inhibitors such as TAPLEO.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine 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 "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9. Overdose

In overdose, side effects may be elicited or exacerbated. Appropriate symptomatic and supportive treatment should be initiated as dictated by the patient's clinical status. The removal of TAPLEO by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 21.2 Oral hypoglycaemics

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 subjects. 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.

Distribution:

Dapagliflozin is approximately 91 % protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment).

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 subjects. 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 [^{14}C]- 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 [^{14}C]-dapagliflozin dose, 96 % was recovered, 75 % in urine and 21 % in faeces. In faeces, approximately 15 % of the dose was excreted as parent compound.

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 subjects. 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 subjects. 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 subjects. 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 subjects (≥ 120 kg, n = 91) were estimated to be 78,3% [90 % CI:78,2; 83,2 %] of those of reference subjects 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.

Subjects with low body weights (< 50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low body weight subjects were estimated to be 29 % higher than subjects 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

Tablet core

Crospovidone

Lactose anhydrous

Magnesium stearate

Microcrystalline cellulose

Silicon dioxide

Film-coating

Hydrolysed polyvinyl alcohol

Titanium dioxide

Polyethylene glycol

Talc

Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months Bristol-Myers Squibb

36 Months AstraZeneca Pharmaceuticals

Store at or below 30 °C.

6.4. Special precautions for storage

This medicine does not require any special storage conditions.

6.5. Nature and contents of container

Silver aluminium/aluminium foil blister packs of 14, 28, 30, 90 and 98 tablets packed in a carton. 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

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2, Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg

2191

8. REGISTRATION NUMBER(S)

TAPLEO 5: 56/21.2/0611

TAPLEO 10: 56/21.2/0612

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

TBA

10. DATE OF REVISION OF THE TEXT

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