

Approved Professional Information for Medicines for Human Use:

GLUDAPZIN 5/10

GLUDAPZIN IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES. GLUDAPZIN IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES AND NOT INDICATED FOR THE TREATMENT OF ANY OTHER CONDITIONS EXCEPT TYPE 2 DIABETES.

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

Patient 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. GLUDAPZIN 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 GLUDAPZIN.

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

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GLUDAPZIN 5 film-coated tablets

GLUDAPZIN 10 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GLUDAPZIN 5: Each film-coated tablet contains 5 mg dapagliflozin.

GLUDAPZIN 10: Each film-coated tablet contains 10 mg dapagliflozin.

Contains sugar: lactose monohydrate.

Each 5 mg film-coated tablets contains 25 mg lactose monohydrate.

Each 10 mg film-coated tablets contains 50 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

GLUDAPZIN 5

Light yellow to yellow coloured round shaped film-coated tablets debossed with "D" on one side and "5" on the other side.

GLUDAPZIN 10

Light yellow to yellow coloured diamond shaped film-coated tablets debossed with "D" on one side and "10" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GLUDAPZIN is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy

As an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus.

Add-on combination therapy

In combination 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.

4.2 Posology and method of administration

Posology

Monotherapy and add-on combination therapy

The recommended dose is 10 mg GLUDAPZIN 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.

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

Special populations

Elderly population

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

Renal impairment

No dosage adjustment for GLUDAPZIN is indicated for mild renal impairment. The efficacy of GLUDAPZIN

is dependent on renal function. GLUDAPZIN should not be used in patients with moderate to severe renal impairment (defined as eGFR < 60 mL/min/1,73 m² by MDRD or CrCl < 60 mL/min by Cockcroft-Gault) (see section 4.3, 4.4 and 4.8).

Monitoring of renal function is recommended as follows:

- Prior to initiation of GLUDAPZIN 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 CrCl < 60 mL/min or eGFR < 60 mL/min/1,73 m², GLUDAPZIN treatment should be discontinued.

Hepatic impairment

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

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 GLUDAPZIN may be appropriate (see section 4.4 and 4.8).

Paediatric population

Safety and efficacy of GLUDAPZIN in paediatric and adolescent patients have not been established.

Method of administration

GLUDAPZIN can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Moderate and severe renal impairment with GFR < 60 mL/min, end stage renal failure or patients on dialysis.
- Diabetes Mellitus Type 1
- Pregnant women or women who are breastfeeding their infants (see section 4.6).

4.4 Special warnings and precautions for use

Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances

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

Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure (see section 5.1), which may be more pronounced in patients with very high blood glucose concentrations.

Dapagliflozin as in GLUDAPZIN is not recommended for use in patients receiving loop diuretics (see section 4.5) or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness).

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

For patients receiving dapagliflozin as in GLUDAPZIN, in case of intercurrent conditions that may lead to volume depletion, 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 4.8).

Diabetic ketoacidosis (DKA)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with caution in patients with increased

risk of DKA. Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 1 diabetes patients, 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.

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.

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

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 as in GLUDAPZIN may be restarted when the ketone values are normal, and the patient's condition has stabilised.

Type 2 diabetes mellitus

Cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with 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).

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

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.

Before initiating dapagliflozin as in GLUDAPZIN

Before starting treatment, patients should be evaluated with respect to DKA risk.

Dapagliflozin as in GLUDAPZIN should not be initiated when patients are at a higher risk of DKA, such as:

- Patients with low insulin needs.
- Patient not on optimal insulin dose or who have recent issues with noncompliance or recurrent errors with insulin dosing and who are unlikely to maintain adequate insulin dosing.
- Patients with increased insulin requirements due to acute medical illness or surgery.
- Patients who insist on maintaining caloric restriction, carbohydrate restriction or ketogenic diet or who chronically under-dose insulin (e.g. in order to remain in a lipolytic state).
- Patients with recent or recurrent history of DKA.
- Patients with elevated ketones levels (BHB reading is greater than 0,6 mmol/L or urine ketones one plus (+)). If ketones are elevated (blood beta-hydroxybutyrate reading 0,6 mmol/L or greater), treatment with dapagliflozin as in GLUDAPZIN should not be started until the ketone levels are normal (see section 4.2).
- Patients unable or unwilling to monitor ketones.
- Patients with excessive alcohol consumption or who use illicit drugs.
- Patients using an insulin infusion pump have a higher risk of DKA and should be experienced with pump use, common trouble-shooting strategies when interruptions of insulin delivery via pump occur (issues with insertion site, clogged tubing, empty reservoir, etc.) and use of supplemental insulin injections with pen or syringe as needed in case of pump failure. Patients should consider monitoring ketones levels three to four hours after changing pump materials. Patients using a pump should also check their ketone levels with any suspected insulin interruption, regardless of blood glucose levels. Insulin injections should be given within 2 hours of an unexplained high blood glucose/ketone value and dapagliflozin as in GLUDAPZIN treatment should be interrupted.
- The patients should be educated on the risk of DKA, emphasising that DKA could occur even when blood glucose levels are below 14 mmol/L (250 mg/dL).
- The patient should be informed how to recognise the risk factors which can predispose to ketosis (including starvation ketosis) and DKA and how to recognise DKA signs or symptoms.
- Dapagliflozin as in GLUDAPZIN should only be given to patients who are able to monitor ketone

levels and are educated in when it is most appropriate to do so.

- Dapagliflozin as in GLUDAPZIN should only be given to patients with access to ketone testing materials and immediate access to a clinician if blood or urine ketones are elevated.
- The patients should be educated on what actions to take when ketosis/DKA is suspected and when to discontinue dapagliflozin therapy (see section 4.2).
- DKA should be treated as per standard of care. Supplemental carbohydrate may be required in addition to hydration and additional rapid insulin.

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

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.

During treatment with dapagliflozin as in GLUDAPZIN

- Insulin therapy should be continuously optimised.
- When needed to prevent hypoglycaemia, insulin dose reduction should be done cautiously to avoid ketosis and DKA (see section 4.2).
- In the event of a marked reduction of insulin need, discontinuation of dapagliflozin as in GLUDAPZIN should be considered.

Ketone monitoring

The patient should be advised to test their ketone level (urine or blood) if signs or symptoms of ketoacidosis occur. Measurement of blood ketone levels is preferred to urine. Ketones should be monitored on a regular basis during the initial one to two weeks, then the frequency of ketone level testing should be individualised, according to the patient's lifestyle and/or risk factors (see section 4.2). Ketone levels should be also checked in situations that may predispose to or increase risk of DKA.

Patients must be informed about what actions to take if ketone levels are elevated. The recommended actions are listed in Table 1 (see section 4.2)

Necrotising fasciitis of the perineum (Fournier's gangrene)

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 less frequent, 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, GLUDAPZIN should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Renal impairment

The glycaemic efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment (see section 4.2). Reported clinical data for subjects with moderate renal impairment (GFR < 60 mL/min), revealed that a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo.

GLUDAPZIN should not be initiated in patients with a GFR < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. Dapagliflozin has not been studied in severe renal impairment (GFR < 30 mL/min) or end-stage renal disease (ESRD).

Monitoring of renal function is recommended as follows:

- Prior to initiation of dapagliflozin and at least yearly, thereafter (see sections 4.2, 4.8, 5.1 and 5.2).
- Prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.
- For renal function with GFR < 60 mL/min, at least 2 to 4 times per year.

Hepatic impairment

There is limited data available in reported clinical trials in patients with hepatic impairment. Dapagliflozin

Austell Pharmaceuticals (Pty) Ltd, 560431-2, GLUDAPZIN, film-coated tablets, 5 mg and 10 mg exposure is increased in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infection. Temporary interruption of dapagliflozin as in GLUDAPZIN should be considered when treating pyelonephritis or urosepsis.

Elderly (≥ 65 years)

Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicine 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, 4.4, 4.8 and 5.1).

Cardiac failure

Experience in NYHA class I-II is limited, and there is no reported experience in clinical studies with dapagliflozin in NYHA class III-IV.

Lower limb amputations

Cases of lower limb amputation (primarily of the toe) has been reported in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot care.

Urine laboratory assessments

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

Excipients: lactose intolerance

GLUDAPZIN contains lactose: patients with rare hereditary problems of galactose intolerance, the Lapp

lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Diuretics

Dapagliflozin 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).

In patients with type 1 diabetes mellitus and a known risk of frequent or severe hypoglycaemia, it may be necessary to reduce the insulin dose at the time of initiating treatment with dapagliflozin to decrease the risk of hypoglycaemia. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA (see section 4.2).

Pharmacokinetic interactions

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

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

Effect of other medicines on dapagliflozin

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

Reported results for coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) indicated an approximately 20 % decrease in dapagliflozin systemic exposure (AUC), 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.

Coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), reportedly shown an approximate 55 % increase in dapagliflozin systemic exposure, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicines

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 approximately 20 % and 30 % increase in AUC of simvastatin and simvastatin acid, respectively. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

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

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

GLUDAPZIN is contraindicated in pregnancy (see section 4.3).

Reported animal studies in rats indicated toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy and was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny. Therefore, when pregnancy is detected, treatment with dapagliflozin should be discontinued.

Breastfeeding

Mothers on GLUDAPZIN should not breastfeed their infants (see section 4.3).

Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. A risk to the new-borns or infants cannot be excluded. Dapagliflozin should not be used while breastfeeding. Exposure to GLUDAPZIN must be avoided during the first 2 years of life.

Fertility

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

4.7 Effects on ability to drive and use machines

GLUDAPZIN has no or negligible influence on the ability to drive and use machines.

However, GLUDAPZIN may cause dizziness (due to blood volume and/or diastolic blood pressure lowering) or cause hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin (see section 4.8). Patients must be alerted to determine the effect of the GLUDAPZIN and possible low blood pressure or low blood sugar levels on their ability to drive or use machines.

4.8 Undesirable effects

Tabulated list of Adverse Drug Reactions (ADRs)

The following adverse reactions have been identified in reported placebo-controlled clinical trials. ADRs were not reported to be dose-related.

System Organ Class	Frequency		
	Frequent	Less Frequent	Not known
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 sulphonylurea or insulin), Diabetic ketoacidosis (when used in type 1 diabetes mellitus)	Volume depletion, Thirst, Diabetic ketoacidosis (when used in type 2 diabetes mellitus)	
Nervous system disorders	Dizziness		
Gastrointestinal disorders		Constipation, Dry mouth	

Skin and subcutaneous tissue disorders	Rash	Angioedema	
Musculoskeletal and connective tissue disorders	Back pain		
Renal and urinary disorders	Dysuria, Polyuria, Glucosuria	Nocturia	
Reproductive system and breast disorders		Vulvovaginal pruritus, Pruritus genital	
Investigations	Haematocrit increased, Creatinine renal clearance decreased, Dyslipidaemia	Blood creatinine increased, Blood urea increased, Weight decreased	

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. Healthcare professionals 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.

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Suspected adverse reactions can also be reported directly to the HCR via medsafety@ustell.co.za

4.9 Overdose

Signs and symptoms

In overdosage, side effects may be elicited or exacerbated (see section 4.8).

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: Drugs used in diabetes, sodium-glucose co-transporter 2 (SGLT2) inhibitors

ATC Code: A10BK01

Dapagliflozin is a reversible inhibitor of sodium glucose co-transporter 2 (SGLT2). SGLT2 is selectively expressed in the kidney and is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycaemia in type 2 diabetes mellitus, reabsorption of filtered glucose continues. 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.

Urinary glucose excretion (glycosuria) induced by dapagliflozin is associated with caloric loss and reduction in weight. 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. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with

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mild diuresis and transient natriuresis.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 3000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

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

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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 $\text{AUC}_{(0-12\text{h})}$] 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 GYP 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

As per reported clinical data, steady-state (20 mg once daily dapagliflozin for 7 days) patients with type 2 diabetes mellitus and mild, moderate or severe renal impairment had mean systemic exposures of dapagliflozin that were higher 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 was lower in

Austell Pharmaceuticals (Pty) Ltd, 560431-2, GLUDAPZIN, film-coated tablets, 5 mg and 10 mg patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment.

As per reported results the steady-state 24 hour urinary glucose excretion was highly dependent on renal function and between 85 g to 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. There were no reported 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 60 mL/min (see section 4.3).

Hepatic impairment

A reported 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 higher, 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 significantly higher than matched healthy controls. 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.

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.

Paediatric population

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate,

Microcrystalline cellulose,

Crospovidone,

Povidone,

Dichloromethane

Dehydrated alcohol,

Microcrystalline cellulose,

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Magnesium stearate.

Film coating

Opadry AMB II Yellow (talc, titanium dioxide (E171), GMCC Type 1/glycerol esters of fatty acids, sodium lauryl sulfate, iron oxide yellow (E172))

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C

6.5 Nature and contents of container

HDPE Bottles: 30 tablets each are packed in 60cc HDPE Round white Opaque bottles with 33 mm child resistance closure with heat seal and pulp liner for induction seal with silica gel canister.

Blister pack: 10 tablets per blister.

Plain 158 mm aluminium foil 25 µ OPA/45 µ Alu/60µ PVC film as a forming film and peel-push lidding foil (50 GSM paper/12 µ PET/20 µ ALU/7GSM HSL width 156 mm) as the lidding material and the blisters are further packed in cartons.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

GLUDAPZIN 5 film-coated tablets: 56/21.2/0431

GLUDAPZIN 10 film-coated tablets: 56/21.2/0432

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 July 2024

10. DATE OF REVISION OF THE TEXT