DAPAGLIFLOZIN

DAPAVID

10 mg Film-Coated Tablet

Blood Glucose Lowering Drug
(Sodium-Glucose Co-Transporter 2
(SGLT2) Inhibitor)

VIDAP02-0 (PHIL)

FORMULATION
Each film-coated tablet of Dapagliflozin (DAPAVID) contains 10mg of dapagliflozin (as dapagliflozin propanediol).

DESCRIPTION
A yellow colored biconvex, diamond-shaped, film coated tablets with "121" engraved on one side and plain on another side.

PHARMACODYNAMICS
Dapagliflozin belongs to drug class Sodium-glucose co-transporter 2 (SGLT2) inhibitors.
It is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2. The SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. SGLT2 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, reabsorption of filtered glucose continues. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and 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.
Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.
Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

PHARMACOKINETICS
Absorption
Dapagliflozin is rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (Cmax) are usually attained within 2 hours after administration in the fasted state. Absorption at fasted and fed state are not considered to be clinically meaningful. Hence, dapagliflozin can be taken with or without food.

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

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

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

INDICATIONS
Dapagliflozin (DAPAVID) is indicated in adults for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
- As monotherapy when metformin is considered inappropriate due to intolerance.
- In addition to other medicinal products for the treatment of type 2 diabetes.

CONTRAINDICATIONS
Hypersensitivity to the dapagliflozin or to any of the excipients of Dapagliflozin (Dapavid) 10mg Tablets.

WARNINGS AND PRECAUTIONS
Renal impairment
The glycaemic efficacy of Dapagliflozin (DAPAVID) 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. In subjects with moderate renal impairment (GFR < 60 mL/min), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo.
Dapagliflozin (DAPAVID) should not be initiated in patients with a GFR < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. Dapagliflozin (DAPAVID) 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.
- Prior to initiation of concomitant medicinal products 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 experience in clinical studies in patients with hepatic impairment. Dapagliflozin (DAPAVID) exposure is increased in patients with severe hepatic impairment.

Use in patients at risk for volume depletion and/or hypotension
Due to its mechanism of action, Dapagliflozin (DAPAVID) increases diuresis which may lead to the modest decrease in blood pressure. It may be more pronounced in patients with very high blood glucose concentrations.

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

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

Diabetic ketoacidosis
Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with caution in patients with increased risk of diabetic ketoacidosis (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 (DAPAVID), 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. In both cases, treatment with Dapagliflozin (DAPAVID) may be restarted once the patient's condition has stabilised.

Type 2 diabetes mellitus
Rare 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 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.

Type 1 diabetes mellitus
In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. Dapagliflozin (DAPAVID) 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. 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 (DAPAVID) 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 (DAPAVID) should be considered when treating pyelonephritis or urosepsis.

Elderly (≥ 65 years)
Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

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

Cardiac failure
There is no experience in clinical studies with dapagliflozin in NYHA class IV.

Lower limb amputations
An increase in cases of lower limb amputation (primarily of the toe) has been observed 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 Dapagliflozin (DAPAVID) will test positive for glucose in their urine.

Lactose
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Pharmacodynamic interactions

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

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

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

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

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

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) an 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), an increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products
In 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.

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

Pediatric
Interaction studies have only been performed in adults.

PREGNANCY AND LACTATION

Pregnancy
The use of Dapagliflozin (DAPAVID) is not recommended during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with Dapagliflozin (DAPAVID) should be discontinued.

Breast-feeding
Dapagliflozin (DAPAVID) should not be used while breast-feeding.

EFFECTS ON ABILITY TO DRIVER AND USE MACHINES

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

DRUG INTERACTIONS

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

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

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

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

Effect of other medicinal products on dapagliflozin
The pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a slight 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), an increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products
Dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a slight increase in AUC of simvastatin and simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

MAIN SIDE/ ADVERSE EFFECTS

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing surveillance. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Table 1: Adverse Drug Reactions by Frequency and System Organ Class (SOC)

System organ class	Common	Rare	Very rare	Unknown
Infections and infestations	Genital infection[a,b] Urinary tract infection[a,c]		Necrotizing fasciitis of the perineum (Fournier's Gangrene)[b]	
Metabolism and Nutrition Disorders		Diabetic ketoacidosis[a]		
Skin and subcutaneous tissue disorders				Rash[f,g]
Musculoskeletal and Connective Tissue Disorders	Back pain[a]			
Renal Urinary Disorders	Pollakiuria[a] and polyuria[a,d]			

a Identified from comparator's 13 placebo-controlled studies with dapagliflozin 10 mg in type 2 diabetes mellitus including 3 monotherapy, 1 initial combination with metformin, 2 add-on to metformin, 2 add-on to insulin, 1 add-on to pioglitazone, 1 add-on to sitagliptin, 1 add-on to glimepiride, and 2 studies with combination add-on therapy.
b Multiple adverse events terms, information including vulvovaginal infections and candidiasis balanoposthitis, balanitis candida, penile abscess, penile infection, vulval abscess and vaginitis bacterial.
c Multiple adverse events terms, including genitourinary tract infection, cystitis, pyelonephritis, trigonitis, urethritis and prostatitis
d Represents multiple adverse events terms, including polyuria, urine output increased.
e Identified from the comparator's cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.
f Identified during postmarketed use of comparator's dapagliflozin. Because these reactions are reported voluntarily from a population of an uncertain size, it is not always possible to reliably estimate their frequency.
g Rash includes the following preferred terms, listed in order of frequency in comparator's clinical trials: Rash, Rash generalized, Rash pruritic, Rash macular, Rash maculo-papular, Rash pustular, Rash vesicular, Rash erythematous.
h See Warnings and Precautions.

OVERDOSE AND TREATMENT

Symptoms
Orally-administered dapagliflozin has been shown to be safe and well tolerated in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose) for at least 5 days and once-daily doses of up to 100 mg (10 times the maximum recommended human dose) for 2 weeks.

Management
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.

DOSAGE AND ADMINISTRATION

The recommended dose of Dapagliflozin (DAPAVID) is 10mg taken orally once daily at any time of the day regardless of meals.

Type 2 Diabetes Mellitus
Monotherapy and Add-On Combination Therapy
The recommended dose of Dapagliflozin (DAPAVID) is 10mg once daily as monotherapy or as add-on to combination therapy with metformin (with or without a sulfonylurea), a thiazolidinedione, a sulfonylurea, a DPP4 inhibitor (with or without metformin), a GLP-1 receptor agonist (prolonged-release exenatide), when initiated concomitantly with Dapagliflozin (with meformin), or insulin (with or without oral antidiabetic therapy, either metformin plus insulin dual therapy or metformin plus sulfonylurea plus insulin triple therapy).

Initial Combination therapy
The recommended starting doses of Dapagliflozin (DAPAVID) and metformin when used as initial combination therapy are 10mg Dapagliflozin (DAPAVID) plus 500mg metformin once daily. Patients with inadequate glycemic control on this dose should further have their metformin dose increased according to approved local label guidelines.

Special populations
Renal impairment
Dapagliflozin should not be initiated in patients with a glomerular filtration rate [GFR] < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min.
No dose adjustment is required based on renal function.

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

Elderly (≥ 65 years)
In general, no dose adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account.

Paediatric population
The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available.

Note: The information given here is limited. For further information, kindly consult your doctor or pharmacist.

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

Storage: Store at temperatures not exceeding 30°C.

Availability: Alu/Alu Blister Pack x 7's (Box of 28's).

Registration Number: DRP-14039

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