Product Trade Name		Active Ingredients
Dapaveldactin 10mg Film Coated Tablets		Dapagliflozin 10mg

1.4.1 Prescribing Information (summary of product characteristics)

Refer to next pages attached

Manufacturer		Product	
LIPTIS FOR PHARMACEUTICALS AND MEDICAL PRODUCTS (S.A.E.)	LIPTIS Pharmaceuticals	**Trade Name**	Dapaveldactin
		Generic Name	Dapagliflozin
		Dosage Form	Film Coated Tablets

FULL PRESCRIBING INFORMATION 1

INDICATIONS AND USAGE

DAPAVELDACTIN (dapagliflozin) is indicated :

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.
- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.
- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Limitations of Use

- DAPAVELDACTIN is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.1)]*.
- DAPAVELDACTIN is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. DAPAVELDACTIN is likely to be ineffective in this setting based upon its mechanism of action.
- DAPAVELDACTIN is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. DAPAVELDACTIN is not expected to be effective in these populations.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of DAPAVELDACTIN

Assess renal function prior to initiation of DAPAVELDACTIN therapy and then as clinically indicated *[see Warnings and Precautions (5.2)]*.

Assess volume status and, if necessary, correct volume depletion prior to initiation of DAPAVELDACTIN *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6)]*.

2.2 Recommended Dosage

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 1: Recommended Dosage

eGFR (mL/min/1.73 m^2)	Recommended Dose
eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control*. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily*.
eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

* DAPAVELDACTIN is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. DAPAVELDACTIN is likely to be ineffective in this setting based upon its mechanism of action.
hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.

3 DOSAGE FORMS AND STRENGTHS

- DAPAVELDACTIN 5 mg tablets are yellow, biconvex, round, film-coated tablets with “5” engraved on one side and “1427” engraved on the other side.
- DAPAVELDACTIN 10 mg tablets are yellow, biconvex, diamond-shaped, film-coated tablets with “10” engraved on one side and “1428” engraved on the other side.

4 CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to DAPAVELDACTIN, such as anaphylactic reactions or angioedema *[see Adverse Reactions (6.1)]*.
- Patients on dialysis *[see Use in Specific Populations (8.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Ketoacidosis in Patients with Diabetes Mellitus

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including DAPAVELDACTIN *[see Adverse Reactions (6.1)]*. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking DAPAVELDACTIN. DAPAVELDACTIN is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with DAPAVELDACTIN who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with DAPAVELDACTIN may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, DAPAVELDACTIN should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating DAPAVELDACTIN, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing DAPAVELDACTIN for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.

Consider monitoring for ketoacidosis and temporarily discontinuing DAPAVELDACTIN in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting DAPAVELDACTIN.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue DAPAVELDACTIN and seek medical attention immediately if signs and symptoms occur.

5.2 Volume Depletion

DAPAVELDACTIN can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including DAPAVELDACTIN. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating DAPAVELDACTIN in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension, and renal function after initiating therapy.

5.3 Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including DAPAVELDACTIN. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6)]*.

5.4 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. DAPAVELDACTIN may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with DAPAVELDACTIN.

5.5 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life- threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including DAPAVELDACTIN. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death. Patients treated with DAPAVELDACTIN presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue DAPAVELDACTIN, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.6 Genital Mycotic Infections

DAPAVELDACTIN increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections *[see Adverse Reactions (6.1)]*. Monitor and treat appropriately.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Ketoacidosis in Patients with Diabetes Mellitus *[see Warnings and Precautions (5.1)]*
- Volume Depletion *[see Warnings and Precautions (5.2)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.3)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.4)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.5)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6)]*

7 DRUG INTERACTIONS

7.1 Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, DAPAVELDACTIN is not recommended during the second and third trimesters of pregnancy.

Limited data with DAPAVELDACTIN in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes and untreated heart failure in pregnancy

8.2 Lactation

Risk Summary

There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of

DAPAVELDACTIN is not recommended while breastfeeding.

8.4 Pediatric Use

Safety and effectiveness of DAPAVELDACTIN in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No DAPAVELDACTIN dosage change is recommended based on age.

A total of 1424 (24%) of the 5936 DAPAVELDACTIN-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacy of DAPAVELDACTIN in improving glycemic control in type 2 diabetes mellitus. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with DAPAVELDACTIN for glycemic control had adverse reactions of hypotension *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

8.6 Renal Impairment

Patients with diabetes and renal impairment using DAPAVELDACTIN may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment.

9 OVERDOSAGE

There were no reports of overdose during the clinical development program for DAPAVELDACTIN.

The removal of dapagliflozin by hemodialysis has not been studied.

10 Pharmaceutical particulars

10.1 Shelf life

2 years (24 Months)

10.2 Special precautions for storage

Do not store above 30^{o} C

10.3 Nature and contents of container

Carton box containing 1,2,3,or 4 (Al/Al) blisters, each strip of 7 film coated tablets and inner leaflet.

10.4 Special precautions for disposal and other handling

No special requirements for disposal.

11. Marketing Authorization Holder and Manufacturer:
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12. MARKETING AUTHORISATION NUMBER:
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