SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	Product Name : **DIAZAC 5/10** (Dapagliflozin Tablets 5/10 mg)
	1.2 Strength : **DIAZAC 5** Each film-coated tablet contains: Dapagliflozin .....5 mg **DIAZAC 10** Each film-coated tablet contains: Dapagliflozin .....10 mg
	1.3 Pharmaceutical Dosage Form : Tablets
2.	**Qualitative & Quantitative Composition:** **DIAZAC 5** Each film-coated tablet contains: Dapagliflozin .....5 mg Excipients .....q.s. Colours: Yellow Iron Oxide & Titanium Dioxide **DIAZAC 10** Each film-coated tablet contains: Dapagliflozin .....10 mg Excipients .....q.s. Colours: Yellow Iron Oxide & Titanium Dioxide For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:**
	Film coated tablets **DIAZAC 5** Yellow colored round, biconvex film-coated tablet, debossed with "C5" on one side and plain on other side. **DIAZAC 10** Yellow colored round, biconvex film-coated tablet, debossed with "C10" on one side and plain on other side.
4.	**Clinical Particulars**
	Therapeutic Indications: 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

- Dapagliflozin is not recommended for patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- Dapagliflozin 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. Dapagliflozin is likely to be ineffective in this setting based upon its mechanism of action.

Dapagliflozin 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. Dapagliflozin is not expected to be effective in these populations.

4.2 Posology and Method of administration:

Prior to Initiation of Dapagliflozin

Assess renal function prior to initiation of Dapagliflozin therapy and then as clinically indicated.

Assess volume status and, if necessary, correct volume depletion prior to initiation of Dapagliflozin

Recommended Dosage

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

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.

	* Dapagliflozin 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. Dapagliflozin 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. **Pediatric Use** Safety and effectiveness of Dapagliflozin in pediatric patients under 18 years of age have not been established. **Geriatric Use** No Dapagliflozin dosage change is recommended based on age.
	Contraindications: • History of a serious hypersensitivity reaction to dapagliflozin, such as anaphylactic reactions or angioedema. • Patients on dialysis.
	4.4 Special warning and precautions for use: *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 Dapagliflozin. 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 Dapagliflozin. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus. Patients treated with Dapagliflozin 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 Dapagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, dapagliflozin 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 post-marketing 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 dapagliflozin, 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 Dapagliflozin for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing dapagliflozin 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 dapagliflozin.

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

Volume Depletion

Dapagliflozin 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 dapagliflozin. 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 dapagliflozin 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.

Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including Dapagliflozin. 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.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. 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 Dapagliflozin.

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 post-marketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.
Patients treated with dapagliflozin 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 dapagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

	Genital Mycotic Infections Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat appropriately.
	4.5 Interactions with other medicinal products and other forms of Interactions : *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. *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..
	4.6 Pregnancy and Lactation: **Pregnancy** ***Risk Summary*** Based on animal data showing adverse renal effects, Dapagliflozin is not recommended during the second and third trimesters of pregnancy. Limited data with dapagliflozin 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. In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose **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 (see Data). However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in breastfed infants, advise women that use of dapagliflozin is not recommended while breastfeeding. ***Data*** Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.
	4.7 Effects on ability to drive and use machine:

Dapagliflozin 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.

4.8 Undesirable Effects:

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Dapagliflozin has been evaluated in clinical trials in patients with type 2 diabetes mellitus, in patients with heart failure, and in patients with chronic kidney disease. The overall safety profile of dapagliflozin was consistent across the studied indications. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.

These adverse reactions were not present at baseline, occurred more commonly on Dapagliflozin than on placebo, and occurred in at least 2% of patients treated with either Dapagliflozin 5 mg or Dapagliflozin 10 mg.

Table - shows common adverse reactions associated with the use of Dapagliflozin

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	DAPAGLIFLOZIN 5 mg N=1145	DAPAGLIFLOZIN 10 mg N=1193
Female genital mycotic infections*	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections†	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination‡	1.7	2.9	3.8
Male genital mycotic infections§	0.3	2.8	2.7
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females:

Placebo=677, DAPAGLIFLOZIN 5 mg=581, DAPAGLIFLOZIN 10 mg=598).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tractinfection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

‡ Increased urination includes the following adverse reactions, listed in order of frequencyreported: pollakiuria, polyuria, and urine output increased.

§ Genital mycotic infections include the following adverse reactions, listed in order of frequencyreported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. (N for males: Placebo=716, DAPAGLIFLOZIN 5 mg=564, DAPAGLIFLOZIN 10 mg=595).

Volume Depletion

Dapagliflozin causes an osmotic diuresis, which may lead to a reduction in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) in patients with type 2 diabetes mellitus.

Hypoglycemia

Hypoglycemia was more frequent when dapagliflozin was added to sulfonylurea or insulin.

Genital Mycotic Infections

In the glycemic control trials, genital mycotic infections were more frequent with dapagliflozin treatment.
Infections were more frequently reported in females than in males. The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with dapagliflozin and <0.1% of patients treated with placebo.

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with dapagliflozin treatment. In glycemic control studies, serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of dapagliflozin-treated patients. If hypersensitivity reactions occur, discontinue use of Dapagliflozin; treat per standard of care and monitor until signs and symptoms resolve.

Ketoacidosis in Patients with Diabetes Mellitus

In the DECLARE study, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the dapagliflozin-treated group and 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

Laboratory Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of SGLT2 inhibitors, including dapagliflozin causes a small increase in serum creatinine and decrease in eGFR. In patients with normal or mildly impaired renal function at baseline, these changes in serum creatinine and eGFR generally occur within weeks of starting therapy and then stabilize.

	Increase in Hematocrit In the pool of 13 placebo-controlled studies of glycemic control, increases from baseline in mean hematocrit values were observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were −0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg-treated patients. *Increase in Low-Density Lipoprotein Cholesterol* In the pool of 13 placebo-controlled studies of glycemic control, changes from baseline in mean lipid values were reported in dapagliflozin-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and dapagliflozin 10 mg groups, respectively. In the DECLARE study, mean changes from baseline after 4 years were 0.4 mg/dL versus - 4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in dapagliflozin treated and the placebo groups, respectively. *Decrease in Serum Bicarbonate* In a study of concomitant therapy of dapagliflozin 10 mg with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the dapagliflozin and exenatide-extended release treatment groups. *DAPA-HF Heart Failure Study* No new adverse reactions were identified in the DAPA-HF heart failure study. *DAPA-CKD Chronic Kidney Disease Study* No new adverse reactions were identified in the DAPA-CKD study in patients with chronic kidney disease. **Post-marketing Experience** Additional adverse reactions have been identified during post approval use of dapagliflozin in patients with diabetes mellitus. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. • Ketoacidosis • Acute Kidney Injury • Urosepsis and Pyelonephritis • Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) • Rash
	4.9 Overdosage: There were no reports of overdose during the clinical development program for dapagliflozin. It is also reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.
5.	**Pharmacological properties**

	5.1 Pharmacodynamic Properties: **Pharmacodynamics:** Pharmacotherapeutic group: Drugs used in diabetes, sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK01 ***Mechanism of action*** Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and thereby promotes urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity, and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback.
	5.2 Pharmacokinetics Properties: *Absorption* Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food. *Distribution* Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment. *Metabolism* The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma. *Elimination* Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.
	5.3 Preclinical Safety data: *Carcinogenesis, Mutagenesis, Impairment of Fertility* Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10

	mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72-times (males) and 105-times (females) the clinical dose of 10 mg per day, based on AUC exposure. In rats, the highest dose was approximately 131-times (males) and 186-times (females) the clinical dose of 10 mg per day, based on AUC exposure. Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of in vitro clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 μg/mL. Dapagliflozin was negative for clastogenicity in a series of in vivo studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose. There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans. Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708-times and 998-times the maximum recommended human dose in males and females, respectively.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: Microcrystalline Cellulose, Anhydrous Lactose, Polyoxyl 40 Hydrogenated Castor Oil, Isopropyl Alcohol, Colloidal Silicon Dioxide, Crospovidone, Magnesium Stearate, Methylene Chloride, Opadry 03B22227 Yellow. (HPMC2910/Hypromellose 6mPas, Titanium Dioxide (E171), Macrogol MW 400, Iron Oxide Yellow (E172)).
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 24 months
	6.4 Special Precautions for storage: Store below 30°C.
	6.5 Nature and contents of container: 10 tablets in Alu-Alu blister pack, 3 such blisters in a printed carton along with Pack Insert.
	6.6 Special precautions for disposal: Not applicable
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India **Manufacturing Site Address:** Ajanta Pharma Limited Z/103/A, Dahej SEZ II, Bharuch-392 130, Dist. Bharuch, Gujarat State, India

8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** Sep 30, 2021