## 1. Name of medicinal products

Dapagliflozin Tablets 10 mg

## 2. Qualitative and Quantitative Composition

| Sr. No. | Ingredients | Spec. | Label Claim | Qty/ Tablet (in mg) | % Overages | Functions |
|---|---|---|---|---|---|---|
| **Dry Mixing** | | | | | | |
| 1 | Dapagliflozin Propanediol monohydrate Eq. to Dapagliflozin* | IHS | 10 mg | 12.302 | - | Active |
| 2 | Microcrystalline Cellulose** | BP | - | 117.698 | - | Diluent |
| 3 | Lactose | BP | - | 50.00 | - | Diluent |
| 4 | Crospovidone | BP | - | 15.00 | - | Disintegrant |
| 5 | Colloidal Anhydrous silica | BP | - | 2.00 | - | Glidant |
| **Lubrication** | | | | | | |
| 6 | Magnesium Stearate | BP | - | 3.00 | - | Lubricant |
| **Total weight of uncoated tablet: 200.0 mg** | | | | | | |
| **Coating** | | | | | | |
| 7 | Instacoat Aqua II Yellow | IHS | - | 6.00 | 20.00@ | Coating agent |
| 8 | Purified Water*** | BP | - | Q.S. | - | Vehicle |
| **Total weight of coated tablet: 206.0 mg** | | | | | | |

**Note:** 12.300 mg of Dapagliflozin Propanediol monohydrate equivalent to 10.000 mg of Dapagliflozin.
**Qty. to be calculated on basis of assay and LOD.
* Qty. to be compensate.
@ 20% overages are taken to compensate for the process loss.
**BP:** British Pharmacopoeia; **IHS:** In House Specification

## 3. Pharmaceutical form

**Dosage form:** Film coated Tablets

**Description:** Yellow to pale yellow coloured, round shaped, film coated tablets plain on both sides.

## 4. Clinical particulars

### 4.1 Therapeutic indications

**Type 2 diabetes mellitus**

Dapagliflozin is indicated in adults and children aged 10 years and above 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.

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied.

**Heart failure**

Dapagliflozin is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

**Chronic kidney disease**

Dapagliflozin is indicated in adults for the treatment of chronic kidney disease.

## 4.2 Posology and method of administration

**Posology**

**Type 2 diabetes mellitus**

The recommended dose is 10 mg dapagliflozin once daily.

When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulphonyl urea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycemia.

**Heart failure**

The recommended dose is 10 mg dapagliflozin once daily.

In the DAPA-HF study, dapagliflozin was administered in conjunction with other heart failure therapies.

**Chronic kidney disease**

The recommended dose is 10 mg dapagliflozin once daily.

In the DAPA-CKD study, dapagliflozin was administered in conjunction with other chronic kidney disease related therapies

**Special populations**

**Renal impairment**

No dose adjustment is required based on renal function.

It is not recommended to initiate treatment with dapagliflozin in patients with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m$^2$ .

In patients with type 2 diabetes mellitus, the glucose lowering efficacy of dapagliflozin is reduced when eGFR is< 45 mL/min/1.73m$^2$, and is likely absent in patients with severe renal impairment. Therefore, if eGFR falls below 45 mL/min/1.73m$^2$, additional glucose lowering treatment should be considered in patients with type 2 diabetes mellitus.

**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)**
No dose adjustment is recommended based on age.
**Paediatric population**
No dose adjustment is required for the treatment of type 2 diabetes mellitus in children aged 10 years and above. No data are available for children below 10 years of age.
The safety and efficacy of dapagliflozin for the treatment of heart failure or for the treatment of chronic kidney disease in children <18 years have not yet been established. No data are available.

**Method of administration**
Oral use only.

## 4.1 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use
**Renal impairment**
There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m$^2$, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m$^2$. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m$^2$
The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with eGFR < 45 mL/min/1.73m$^2$ and is likely absent in patients with severe renal impairment.
In patients with moderate renal impairment (eGFR < 60 mL/min/1.73m$^2$), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo.
**Hepatic impairment**
There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin 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 increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. 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 is recommended for patients who develop volume depletion until the depletion is corrected.

**Diabetic ketoacidosis**

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with sodium-glucose co-transporter 2 (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).

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.

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

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

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

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g., 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. SGLT2 inhibitors should be used with caution in these patients.

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.

In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. Dapagliflozin 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 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 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**

Experience with dapagliflozin in NYHA class IV is limited.

**Chronic kidney disease**

There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria.

Dapagliflozin has not been studied for the treatment of chronic kidney disease in patients with polycystic kidney disease, glomerulonephritis with flares (lupus nephritis or ANCA-associated vasculitis), ongoing or recent requirements of cytotoxic, immunosuppressive or other immunomodulating renal therapy, or in patients who received an organ transplant.

**Lower limb amputations**

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

**Urine laboratory assessments**

Due to its mechanism of action, patients taking Dapagliflozin 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 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**

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) a 22% 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), a 55% 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 may increase renal lithium excretion and the blood lithium levels may be decreased. Serum concentration of lithium should be monitored more frequently after dapagliflozin initiation and dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

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. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

**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.
**Paediatric population**
Interaction studies have only been performed in adults.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**
There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see section 5.3). Therefore, the use of dapagliflozin is not recommended during the second and third trimesters of pregnancy.
When pregnancy is detected, treatment with dapagliflozin should be discontinued.
**Breast-feeding**
It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. 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 newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.
**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

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

**Summary of the safety profile**
**Type 2 diabetes mellitus**
In the clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.
The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.
In the dapagliflozin cardiovascular outcomes study in type 2 diabetes mellitus (DECLARE study, see section 5.1), 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a

median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections.

**Heart failure**

In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF study), 2,368 patients were treated with dapagliflozin 10 mg and 2,368 patients with placebo for a median exposure time of 18 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥ 30 mL/min/1.73 $m^2$.

The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

**Chronic kidney disease**

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR≥25 to ≤75 mL/min/1.73$m^2$. Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 $m^2$.

The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin.

**Tabulated list of adverse reactions**

The following adverse reactions have been identified in the placebo-controlled clinical studies and post marketing 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 reactions in placebo-controlled clinical studies[a] and post marketing experience**

| System organ class | Very common | Common* | Uncommon** | Rare | Very rare |
|---|---|---|---|---|---|
| Infections and infestations | | Vulvovaginitis, balanitis and related genital infections[*,b,c]<br>Urinary tract infection[*,b,d] | Fungal infection[**] | | Necrotising fasciitis of the perineum (Fournier's gangrene)[b,i] |

| | | | | | |
|---|---|---|---|---|---|
| Metabolism and nutrition disorders | Hypoglycaemia (when used with SU or insulin)[b] | | Volume depletion[b,e]<br>Thirst[**] | Diabetic ketoacidosis (when used in type 2 diabetes mellitus)[b,i,k] | |
| Nervous system disorders | | Dizziness | | | |
| Gastrointestinal disorders | | | Constipation[**]<br>Dry mouth[**] | | |
| Skin and subcutaneous tissue disorders | | Rash[j] | | | Angioedema |
| Musculoskeletal and connective tissue disorders | | Back pain[*] | | | |
| Renal and urinary disorders | | Dysuria<br>Polyuria[*,f] | Nocturia[**] | | Tubulointerstitial nephritis |
| Reproductive system and breast disorders | | | Vulvovaginal pruritus[**]<br>Pruritus genital[**] | | |
| Investigations | | Haematocrit increased[g]<br>Creatinine renal clearance decreased during initial treatment[b]<br>Dyslipidaemia[h] | Blood creatinine increased during initial treatment[**,b]<br>Blood urea increased[**]<br>Weight decreased[**] | | |

**a** The table shows up to 24-week (short-term) data regardless of glycaemic rescue.
**b** See corresponding subsection below for additional information.
**c** Vulvovaginitis, balanitis and related genital infections includes, e.g., the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal,

vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

**d** Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

**e** Volume depletion includes, e.g., the predefined preferred terms: dehydration, hypovolaemia, hypotension.

**f** Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

**g** Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus –0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.

**h** Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%.

**i** See section 4.4

**j** Adverse reaction was identified through post marketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.

**k** Reported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.

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

**Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

**Description of selected adverse reactions**

**Vulvovaginitis, balanitis and related genital infections**

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the DECLARE study, the numbers of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

In the DAPA-HF study, no patient reported serious adverse events of genital infections in the dapagliflozin group and one in the placebo group. There were 7 (0.3%) patients with adverse events leading to discontinuations due to genital infections in the dapagliflozin group and none in the placebo group.
In the DAPA-CKD study, there were 3 (0.1%) patients with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group. Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes.

**Necrotising fasciitis of the perineum (Fournier's gangrene)**
Cases of Fournier's gangrene have been reported post marketing in patients taking SGLT2 inhibitors, including dapagliflozin.
In the DECLARE study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.
**Hypoglycaemia**
The frequency of hypoglycaemia depended on the type of background therapy used in the clinical studies in diabetes mellitus.
For studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia.
In an add-on to glimepiride study, at weeks 24 and 48, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0% and 7.9%, respectively) than in the placebo plus glimepiride group (2.1% and 2.1%, respectively).
In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects treated with dapagliflozin 10 mg plus insulin at weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at weeks 24 and 104. At weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin.
In an add-on to metformin and a sulphonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea.

In the DECLARE study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.
In the DAPA-HF study, major events of hypoglycaemia were reported in 4 (0.2%) patients in both the dapagliflozin and placebo treatment groups and observed only in patients with type 2 diabetes mellitus.
In the DAPA-CKD study, major events of hypoglycaemia were reported in 14 (0.7%) patients in the dapagliflozin group and 28 (1.3%) patients in the placebo group and observed only in patients with type 2 diabetes mellitus.

**Volume depletion**
In the 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo.
In the DECLARE study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and angiotensin converting enzyme inhibitors (ACE-I)/angiotensin II type 1 receptor blockers (ARB) use. In patients with eGFR < 60 mL/min/1.73 $m^2$ at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.
In the DAPA-HF study, the numbers of patients with events suggestive of volume depletion were 170 (7.2%) in the dapagliflozin group and 153 (6.5%) in the placebo group. There were fewer patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group (23 [1.0%]) compared with the placebo group (38 [1.6%]). Results were similar irrespective of presence of diabetes at baseline and baseline eGFR.
In the DAPA-CKD study, the numbers of patients with events suggestive of volume depletion were 120 (5.6%) in the dapagliflozin group and 84 (3.9%) in the placebo group. There were 16 (0.7%) patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group and 15 (0.7%) patients in the placebo group.

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

In the DAPA-HF study, events of DKA were reported in 3 patients with type 2 diabetes mellitus in the dapagliflozin group and none in the placebo group.
In the DAPA-CKD study, events of DKA were not reported in any patient in the dapagliflozin group and in 2 patients with type 2 diabetes mellitus in the placebo group.

**Urinary tract infections**

In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.7% versus 3.5%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment.
These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.
In the DECLARE study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.
In the DAPA-HF study, the numbers of patients with serious adverse events of urinary tract infections were 14 (0.6%) in the dapagliflozin group and 17 (0.7%) in the placebo group. There were 5 (0.2%) patients with adverse events leading to discontinuations due to urinary tract infections in each of the dapagliflozin and placebo groups.
In the DAPA-CKD study, the numbers of patients with serious adverse events of urinary tract infections were 29 (1.3%) in the dapagliflozin group and 18 (0.8%) in the placebo group. There were 8 (0.4%) patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 3 (0.1%) in the placebo group. The numbers of patients without diabetes reporting serious adverse events of urinary tract infections or adverse events leading to discontinuation due to urinary tract infections were similar between treatment groups (6 [0.9%] versus 4 [0.6%] for serious adverse events, and 1 [0.1%] versus 0 for adverse events leading to discontinuation, in the dapagliflozin and placebo groups, respectively).

**Increased creatinine**

Adverse reactions related to increased creatinine were grouped (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). In the 13-study safety pool, this grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR $\geq$ 60 mL/min/1.73 $m^2$) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR $\geq$ 30 and < 60 mL/min/1.73 $m^2$ (18.5% dapagliflozin 10 mg versus 9.3% placebo).
Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of $\leq$ 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.
In the DECLARE study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 $m^2$), eGFR decreased over time in both treatment groups. At 1-year,

mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.
In the DAPA-HF study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial decrease in mean eGFR was -4.3 mL/min/1.73 $m^2$ in the dapagliflozin group and -1.1 mL/min/1.73 $m^2$ in the placebo group. At 20 months, change from baseline in eGFR was similar between the treatment groups: -5.3 mL/min/1.73 $m^2$ for dapagliflozin and -4.5 mL/min/1.73 $m^2$ for placebo.
In the DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was -4.0 mL/min/1.73 $m^2$ in the dapagliflozin group and -0.8 mL/min/1.73 $m^2$ in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 $m^2$ in the dapagliflozin group and -8.6 mL/min/1.73 $m^2$ in the placebo group.

**Paediatric population**

The dapagliflozin safety profile observed in a clinical study in children aged 10 years and above with type 2 diabetes mellitus was similar to that observed in the studies in adults.

## 4.9 Overdose

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.
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

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

**ATC code:** A10BK01

**Mechanism of action:**

Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2.
Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF and DAPA-CKD studies.
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 GFR. Thus, in subjects with normal blood glucose and/or low GFR, dapagliflozin has a low propensity to cause hypoglycaemia, as the amount of filtrated glucose is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.
The SGLT2 is selectively expressed in the kidney. 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.

## 5.2 Pharmacokinetic properties

### Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations ($C_{max}$) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin $C_{max}$ and $AUC_{\tau}$ values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng h/mL, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. 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. Hence, Dapagliflozin can be administered with or without food.

**Distribution**

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g., renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 liters.

**Biotransformation**

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.

**Linearity/non-linearity**

Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

**Special populations**

**Renal impairment**

At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of haemodialysis on dapagliflozin exposure is not known. The effect of reduced renal function on systemic exposure was evaluated in a population pharmacokinetic model. Consistent with previous results, model predicted AUC was higher in patients with chronic kidney disease compared with patients with normal renal function, and was not meaningfully different in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes.

**Hepatic impairment**

In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean Cmax and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean $C_{max}$ and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

**Elderly (≥ 65 years)**

There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

**Paediatric population**

Pharmacokinetics and pharmacodynamics (glucosuria) in children with type 2 diabetes mellitus aged 10-17 years were similar to those observed in adults with type 2 diabetes mellitus.

**Gender**

The mean dapagliflozin AUCss in females was estimated to be about 22% higher than in males.

**Race**

There were no clinically relevant differences in systemic exposures between White, Black or Asian races.

**Body weight**

Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.

**Elimination**

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. The mean total systemic clearance of dapagliflozin administered intravenously was 207 mL/min. 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 faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

**Reproductive and developmental toxicity**

Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate study of pre- and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed in utero and throughout

lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin exposures were 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29 times the human values at the maximum recommended human dose). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The no observed adverse effect level (NOAEL) for developmental toxicity, the lowest dose tested, is associated with a maternal systemic exposure multiple that is approximately 19 times the human value at the maximum recommended human dose.

In additional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested; the highest dose tested is associated with a systemic exposure multiple of approximately 1,191 times the maximum recommended human dose. In rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose

## 6. Pharmaceutical particulars

### 6.1 List of excipients

- Microcrystalline Cellulose BP
- Lactose BP
- Crospovidone BP
- Colloidal Anhydrous Silica BP
- Magnesium Stearate BP
- Instacoat Aqua II Yellow IHS
- Purified Water BP

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 Months

### 6.4 Special precautions for storage

Do not store above 30ºC. Protect from light.

**6.5 Nature and contents of container**

Alu/Alu Blister.

**6.6 Special precautions for disposal and other handling**

No special requirements.

**7. Marketing authorization holder**

Ratnatris Pharmaceuticals Pvt. Ltd.
Survey no. 416, At- Indrad Taluka-Kadi,
Dist-Mehsana, Pin-382715
Gujarat, India

**8. Marketing authorisation number(s)**

Not Applicable

**9. Date of first authorisation/renewal of the authorization**

Not Applicable

**10. Date of revision of the text**

Not Applicable