# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Dapagliflozin Tablets 5mg
DAPZIN-5

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains: Dapagliflozin.....5 mg

Excipient with known effect: Each 5 mg tablet contains 25.285 mg of lactose anhydrous.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film coated tablet

*Dapagliflozin-5mg*

White to off-white, round, biconvex, seal coated tablets, debossed with 'D1' on one face andplain on other face

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Type 2 diabetes mellitus

Dapagliflozin is indicated in adults for the treatment of insufficiently controlled type 2diabetes 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 and cardiovascular events, and the populations studied.
*Type 1 diabetes mellitus*

Dapagliflozin is indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m2, when insulin

alone does not provide adequate glycaemic control despite optimal insulin therapy.'

**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 sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

*Type 1 diabetes mellitus*

Treatment with Dapagliflozin is to be initiated and supervised by specialists in type 1 diabetes.The recommended dose is 5 mg once daily.
Dapagliflozin must only be administered as an adjunct to insulin.

*Before initiating treatment with dapagliflozin:*

- Risk factors for diabetic ketoacidosis (DKA) should be assessed
- It should be ensured that ketone levels are normal. If ketones are elevated (blood beta-hydroxybutyrate reading greater than 0.6 mmol/L or urine ketones one plus (+)), treatment with dapagliflozin should not be started until the ketone levels are normal.
- It should be ensured that the patient demonstrates the ability to monitor ketone levels.
- It is recommended that patients obtain several baseline ketone levels over one to two weeks prior to initiation of dapagliflozin therapy, and patients should become familiar with how their behaviour and circumstances affect their ketone levels.
- Patients should be informed, in a dedicated education session, on the risk of DKA, how to recognize DKA risk factors, signs or symptoms, how and when to monitor ketone levels and what actions to take at elevated ketone readings.
- Correction of volume depletion prior to initiation of dapagliflozin is recommended in patients with this condition.

In order to avoid hypoglycaemia with the first dose of dapagliflozin, a 20% reduction in the first mealtime bolus insulin may be considered. Subsequent bolus doses should be adjusted

individually based on blood glucose results. No reduction in basal insulin is recommended when initiating dapagliflozin. Subsequently, basal insulin should be adjusted based on blood glucose results. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA.

*Ketone monitoring during treatment:*

During the initial one to two weeks of treatment with dapagliflozin, ketones should be monitored on a regular basis, then the frequency of ketone level testing should be individualized, according to the patient's lifestyle and/or risk factors.

Patients should be informed about what actions to take if ketone levels are elevated. The recommended actions are listed in Table 1. Measurement of blood ketone levels is preferred to urine.

**Table 1**

| **Clinical stage** | **Blood Ketone (beta-hydroxybutyrate)** | **Urine Ketone** | **Actions** |
|---|---|---|---|
| Ketonemia | 0.6-1.5 mmol/L | Trace or Small<br>+ | The patient may need to take extra insulin and drink water. The patient should measure blood glucose and consider taking extra carbohydrates if the glucose levels are normal or low. Ketone levels should be measured againafter two hours.<br>The patient should immediately seekmedical advice and stop taking dapagliflozin if levels persist and symptoms present. |
| Impending DKA | > 1.5-3.0 mmol/L | Moderate<br>++ | The patient should immediately seekmedical advice and stop taking dapagliflozin.<br>The patient may need to take extra |

| | | | |
|---|---|---|---|
| | | | insulin and drink water. The patient should measure blood glucose and consider taking extra carbohydrates if the glucose levels are normal or low. Ketone levels should be measured againafter two hours. |
| Probable DKA | > 3.0 mmol/L | Large to very large<br>+++ / ++++ | The patient should go to emergencydepartment without delay and stop taking dapagliflozin.<br>The patient may need to take extra insulin and drink water. The patient should measure blood glucose and consider taking extra carbohydrates ifthe glucose levels are normal or low. |

*Special populations*

*Renal impairment*

Dapagliflozin should not be initiated in patients with a glomerular filtration rate [GFR] < 60mL/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 welltolerated, the dose may be increased to 10 mg when indicated.

*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.

***Method of administration***

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

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients

**4.4 Special warnings and precautions for use**

*Renal impairment*

The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 $m^2$), 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 is not recommended for use in patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 $m^2$). Dapagliflozin has not been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 $m^2$) orend-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 approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 $m^2$, dapagliflozin treatment should be discontinued.

*Hepatic impairment*

There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.

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

Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure, which may be more pronounced in patients with very high blood glucose concentrations.
Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness).
Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressurecould pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or elderly patients.
For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, and 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). It is not known if DKA is more likely to occur with higher doses of dapagliflozin.

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, treatment with dapagliflozin should be discontinued immediately.
Treatment should be interrupted in patients who are hospitalized for major surgical procedures oracute serious medical illnesses. In both cases, treatment with dapagliflozin may be restarted oncethe patient's condition has stabilized.

*Type 1 diabetes mellitus*

In type 1 diabetes mellitus studies with dapagliflozin, patients had a higher number of DKA events compared with the placebo group.

*Before initiating dapagliflozin*

Before starting treatment, patients should be evaluated with respect to DKA risk.
Dapagliflozin should not be initiated when patients are at a higher risk of DKA, such as:

- Patients with low insulin needs.
- Patient not on optimal insulin dose or who have recent issues with noncompliance or recurrent errors with insulin dosing and who are unlikely to maintain adequate insulin dosing.
- Patients with increased insulin requirements due to acute medical illness or surgery.
- Patients who insist on maintaining caloric restriction, carbohydrate restriction or ketogenicdiet or who chronically under-dose insulin (e.g. in order to remain in a lipolytic state).
- Patients with recent or recurrent history of DKA.
- Patients with elevated ketones levels (BHB reading is greater than 0.6 mmol/L or urine ketones one plus (+)). If ketones are elevated (blood beta-hydroxybutyrate reading 0.6 mmol/L or greater), treatment with dapagliflozin should not be started until the ketone levels are normal
- Patients unable or unwilling to monitor ketones.
- Patients with excessive alcohol consumption or who use illicit drugs.

Patients using an insulin infusion pump have a higher risk of DKA and should be experienced with pump use, common trouble-shooting strategies when interruptions of insulin delivery via pump occur (issues with insertion site, clogged tubing, empty reservoir, etc.) and use of supplemental insulin injections with pen or syringe as needed in case of pump failure. Patients

should consider monitoring ketones levels three to four hours after changing pump materials. Patients using a pump should also check their ketone levels with any suspected insulin interruption, regardless of blood glucose levels. Insulin injections should be given within 2 hours of an unexplained high blood glucose/ketone value and dapagliflozin treatment should be interrupted.

- The patients should be educated on the risk of DKA, emphasizing that DKA could occur even when blood glucose levels are below 14 mmol/L (250 mg/dL).
- The patient should be informed how to recognize the risk factors which can predispose to ketosis (including starvation ketosis) and DKA and how to recognize DKA signs or symptoms.
- Dapagliflozin should only be given to patients who are able to monitor ketone levels and are educated in when it is most appropriate to do so.
- Dapagliflozin should only be given to patients with access to ketone testing materials and immediate access to a clinician if blood or urine ketones are elevated.
- The patients should be educated on what actions to take when ketosis/DKA is suspected and when to discontinue dapagliflozin therapy
- DKA should be treated as per standard of care. Supplemental carbohydrate may be required in addition to hydration and additional rapid insulin

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

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.

*During treatment with dapagliflozin:*

- Insulin therapy should be continuously optimized.
- When needed to prevent hypoglycaemia, insulin dose reduction should be done cautiously to avoid ketosis and DKA
- In the event of a marked reduction of insulin need, discontinuation of dapagliflozin should beconsidered.

*Ketone monitoring:*

The patient should be advised to test their ketone level (urine or blood) if signs or symptoms of ketoacidosis occur. Measurement of blood ketone levels is preferred to urine. Ketones should be monitored on a regular basis during the initial one to two weeks, then the frequency of ketone level testing should be individualized, according to the patient's lifestyle and/or risk factors. Ketone levels should be also checked in situations that may predispose to or increase risk of DKA.
Patients must be informed about what actions to take if ketone levels are elevated. 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 treatedwith 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 will test positive for glucose in their urine.

***Lactose***

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, totallactase 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 therisk of dehydration and hypotension.

*Insulin and insulin secretagogue*

Insulin and insulin secretagogue, 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.

*Pharmacokinetic interactions*

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDPglucuronosyltransferase 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, and 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*

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 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. 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.

***Lactation***

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*

In a pre-specified pooled analysis of 13 placebo-controlled studies, 2,360 subjects were treated with dapagliflozin 10 mg and 2,295 were treated with placebo.
The most frequently reported adverse reaction was hypoglycaemia, which depended on the type of background therapy used in each study. The frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo, with the exceptions of studies with add-on sulphonylurea (SU) and add-on insulin therapies. Combination therapies with sulphonylurea and add-on insulin had higher rates of hypoglycaemia (see *Hypoglycaemia* below).
Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical trials. 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** |
|---|---|---|---|---|
| *Infections and infestations* | | Vulvovaginitis, balanitis and related genital infections [*,b,c]<br>Urinary tract | Fungal infection** | |

| | | | | |
|---|---|---|---|---|
| | | infection [*,b,d] | | |
| *Metabolism and nutrition disorders* | Hypoglycaemia (when used with SU or insulin)[b] | | Volume depletion[b,e]<br>Thirst[**] | Diabetic ketoacidosis[i] |
| *Nervous system disorders* | | Dizziness | | |
| *Gastrointestinal disorders* | | | Constipation[**]<br>Dry mouth[**] | |
| *Skin and subcutaneous tissue disorders* | | Rash[j] | | |
| *Musculoskeletal and connective tissue disorders* | | Back pain[*] | | |
| *Renal and urinary disorders* | | Dysuria<br>Polyuria[*,f] | Nocturia[**]<br>Renal impairment[**,b] | |
| *Reproductive system and breast disorders* | | | Vulvovaginal pruritus[**]<br>Pruritus genital[**] | |
| *Investigations* | | Haematocrit increased[g]<br>Creatinine renalclearance decreased[b]<br>Dyslipidaemia[h] | Blood creatinine increased [**,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 trials: rash, rash generalized, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical trials (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4 %) and all control (1.4%), respectively.

[*]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*

*Hypoglycaemia*

The frequency of hypoglycaemia depended on the type of background therapy used in eachstudy.

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.

*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 dapagliflozin cardiovascular outcomes 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 ACE-I/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.

*Diabetic ketoacidosis*

In the dapagliflozin cardiovascular outcomes 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.

*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; 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 dapagliflozin cardiovascular outcomes 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.
*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). 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 ≥ 60 mL/min/1.73m$^2$) 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 ≥ 30 and < 60 mL/min/1.73m$^2$ (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 ≤ 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment. In the dapagliflozin cardiovascular outcomes 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.

*Clinical studies in type 1 diabetes mellitus*

The safety profile of dapagliflozin in subjects with type 1 diabetes mellitus was similar to the known safety profile of dapagliflozin in subjects with type 2 diabetes mellitus, with the exception of a higher number of DKA events in dapagliflozin-treated subjects in the type 1 diabetes mellitus studies.

*Diabetic ketoacidosis*

In the two placebo-controlled clinical studies of dapagliflozin in type 1 diabetes mellitus, patientswere advised to monitor blood ketones in case of suspected symptoms of DKA and seek medical advice/attention if their self-measured blood ketone reading was ≥ 0.6 mmol/L. In the pooled 52-week data, events of DKA were reported in 22 (4.0%) patients in the dapagliflozin 5 mg group

and 6 (1.1%) patients in the placebo group, with corresponding incidence rates per 100 patient years of 4.62 for dapagliflozin 5 mg and 1.27 for placebo. DKA events occurred evenly distributed over the clinical study period. Inadequate insulin doses (missed insulin dose or insulinpump failure) were the most common precipitating factors. 6 of 23 events of DKA in the dapagliflozin 5 mg group occurred in patients with blood glucose in the euglycemic range (< 14 mmol/L or 250 mg/dL).

### 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 electrolytesand 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 hemodialysis 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 ($K_i$: 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 hyperglycemia 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 (glucuronic 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. Dapagliflozin does not impair normal endogenous glucose production inresponse 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.
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.

***Pharmacodynamic effects***

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day)at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.
This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases inurinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and

amounted to approximately 375 ml/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.
Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/l (-0.87 to -0.33 mg/dl).

**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 values following once daily 10 mg doses of dapagliflozin were 158 ng/ml and628 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 ofdapagliflozin was 118 litres.

***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.

***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 [$^{14}$C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

*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 normalrenal function or mild, moderate or severe renal impairment, respectively. The impact of hemodialysis on dapagliflozin exposure is not known.

*Hepatic impairment*

In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean $C_{max}$ 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 in the paediatric population have not been studied.

*Gender*

The mean dapagliflozin $AUC_{ss}$ 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.

**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 latepregnancy (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 embryo lethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Dapagliflozin Tablets**

Microcrystalline cellulose
Lactose anhydrous
Crospovidone

Polysorbate 80
Colloidal silicon dioxide
Magnesium Stearate
Talc
Polyethylene glycol 6000 PF
Opadry Yellow 85F520253

**6.2 Incompatibilities**

Not Applicable

**6.3 Shelf life**

2 years

**6.4 Special precautions for storage**

Store at 20°C to 25°C

**6.5 Nature and contents of container**

Blister pack of 10's (Alu-Alu)

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

No Special requirement

**7. Marketing Authorization Holder**

MICRO LABS LIMITED

31, Race course roads
Bangalore-560001
INDIA

**8. Market Authorization Number.**

TAN 21 HM 0158

**9. Date of authorization or of the last renewal of the authorization**

29/03/2021

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

March 2021