SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT :

i) Name:
Dapiflozin 5 (Dapagliflozin Tablets 5 mg)
Dapiflozin 10 (Dapagliflozin Tablets 10 mg)

ii) Strength: 10 mg and 20 mg

iii) Pharmaceutical form: Film coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition of 10mg

Ingredients	Specifications	Qty./Tablet (mg)
@Dapagliflozin (Amorphous)	IH	10.000
$Microcrystalline Cellulose (Vivapur 101)	NF 2021 Isuue 1	140.000
Anhydrous Lactose (SuperTab 21 AN),	NF 2021 Isuue 1	50.000
Sepitrap 80	IH	12.500
Low Substituted Hydroxypropyl Cellulose (LH-11)	NF 2021 Isuue 1	10.000
^Acetone	NF 2021 Isuue 1	117.500
Microcrystalline Cellulose (PH-112)	NF 2021 Isuue 1	16.500
Low Substituted Hydroxypropyl Cellulose (LH-11)	NF 2021 Isuue 1	5.000
Colloidal Silicon Dioxide (Aerosil 200 Pharma)	NF 2021 Isuue 1	3.500
Magnesium Stearate	NF 2021 Isuue 1	2.500
**Opadry II Yellow 85F520173	IH	5.000
^Purified Water	USP 2021 Isuue 1/Ph Eur - 10.0	50.000

Remark:
1. @ The actual quantity of Dapagliflozin is to be calculated based on assay

2. $ The actual quantity of Microcrystalline Cellulose (Vivapur 101) varies based on assay and LOD of Dapagliflozin to maintain tablet weight constant.
3. ^ Evaporated during manufacturing process.
4. ** 30% overages are to be taken to compensate the loss during the processing.

Composition of 5 mg

Ingredients	Specifications	Qty./Tablet (mg)
@Dapagliflozin (Amorphous)	IH	5.000
$Microcrystalline Cellulose (Vivapur 101)	NF 2021 Isuue 1	70.000
Anhydrous Lactose (SuperTab 21 AN),	NF 2021 Isuue 1	25.000
Sepitrap 80	IH	6.2500
Low Substituted Hydroxypropyl Cellulose (LH-11)	NF 2021 Isuue 1	5.000
^Acetone	NF 2021 Isuue 1	58.7500
Microcrystalline Cellulose (PH-112)	NF 2021 Isuue 1	8.25
Low Substituted Hydroxypropyl Cellulose (LH-11)	NF 2021 Isuue 1	2.50
Colloidal Silicon Dioxide (Aerosil 200 Pharma)	NF 2021 Isuue 1	1.750
Magnesium Stearate	NF 2021 Isuue 1	1.250
**Opadry II Yellow 85F520173	IH	2.500
^Purified Water	USP 2021 Isuue 1/Ph Eur - 10.0	25.000

Remark:
1. @ The actual quantity of Dapagliflozin is to be calculated based on assay
2. $ The actual quantity of Microcrystalline Cellulose (Vivapur 101) varies based on assay and LOD of Dapagliflozin to maintain tablet weight constant.
3. ^ Evaporated during manufacturing process.
4. ** 30% overages are to be taken to compensate the loss during the processing.

3. PHARMACEUTICAL FORM

Dosage form : Oral Tablets

Description of Dapiflozin 10 mg :
Yellow coloured biconvex, round shaped, film coated tablets with “121” engraved on one side and plain on another side.

Description of Dapiflozin 5 mg :
Yellow coloured biconvex, round shaped, film coated tablets with “120”engraved on one side and plain on another side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Limitations of Use

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

4.2 Posology and method of administration

Prior to initiation of Dapagliflozin

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

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

Recommended Dosage

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

Table 1: Recommended Dosage

eGFR (mL/min/1.73 m²)	Recommended Dose
eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control*. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily*.
eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.
* Dapagliflozin is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m². Dapagliflozin is likely to be ineffective in this setting based upon its mechanism of action. hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.	

4.3 Contraindications

- History of a serious hypersensitivity reaction to Dapagliflozin, such as anaphylactic reactions or angioedema [see **ADVERSE REACTIONS**].
- Patients on dialysis [see **Use In Specific Populations**].

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 Tablets 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 Tablets has not been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 m^2) or end-stage renal disease (ESRD).

Monitoring of renal function is recommended as follows:

- Prior to initiation of dapagliflozin and at least yearly, thereafter.
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter
- For renal function 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.

Treatment of heart failure

There is limited experience with dapagliflozin for the treatment of heart failure in patients with severe renal impairment (GFR < 30 mL/min).

In patients treated with dapagliflozin for both heart failure and type 2 diabetes mellitus, additional glucose-lowering treatment should be considered if GFR falls persistently below 45 mL/min.

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 pressure could 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, 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 hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with dapagliflozin may be restarted once 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 with previous DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.
The safety and efficacy of dapagliflozin in patients with type 1 diabetes have not been established and dapagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.
Urinary tract infections
Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo in a pooled analysis up to 24 weeks. Pyelonephritis was uncommon and occurred at a similar frequency to control. 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.
Type 2 diabetes mellitus
Rare cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL).
In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.

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

Type 1 diabetes mellitus

In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. Dapagliflozin 10 mg 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.

Elderly (≥ 65 years)

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.

In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were transient and reversible.

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion.

Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended.

Cardiac failure

Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV.

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.

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

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. 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 Tablets 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), 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.
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 postmarketing experience

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[*,b,c] 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] Thirst**	Diabetic ketoacidosis (when used in type 2 diabetes mellitus)[b,i,k]	
Nervous system disorders		Dizziness			

Gastrointestinal disorders			Constipation** Dry mouth**		
Skin and subcutaneous tissue disorders		Rash[j]			Angioedema
Musculoskeletal and connective tissue disorders		Back pain*			
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia**		
Reproductive system and breast disorders			Vulvovaginal pruritus** Pruritus genital**		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased during initial treatment[b] Dyslipidaemia[h]	Blood creatinine increased during initial treatment[**,b] Blood urea increased** 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%.
[j]Adverse reaction was identified through postmarketing 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.

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 (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 hyperglycaemia in type 2 diabetes, reabsorption of filtered glucose continues. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. 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 Tablets.

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.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metabolism

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [^{14}C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [^{14}C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (tÂ½) for dapagliflozin is approximately 12.9 hours following a single oral dose of FARXIGA 10 mg.

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 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.

Paediatric population

Pharmacokinetics in the paediatric population have not been studied.

Effects Of Age, Gender, Race, And Body Weight On Pharmacokinetics

Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and thus, no dose adjustment is recommended.

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 (Vivapur 101), Anhydrous Lactose (SuperTab 21 AN), Sepitrap 80, Low Substituted Hydroxypropyl Cellulose (LH-11), Acetone, Microcrystalline Cellulose (PH-112), Colloidal Silicon Dioxide, Magnesium Stearate, Opadry II Yellow 85F520173, Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Pack size for 10 mg

3x10's Alu Alu blister. Carton containing 30 Tablets each with Pack insert in it.

Pack size for 5 mg

3x10's Alu Alu blister. Carton containing 30 Tablets each with Pack insert in it.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER-

Mega Lifesciences Public Company Limited

8. MARKETING AUTHORISATION NUMBER(S)--NA

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION--NA

10. DATE OF REVISION OF THE TEXT—NA

11. DOSIMETRY (IF APPLICABLE)--NA

12. INSTRUCTIONS FOR PREPARATIONS OF RADIOPHARMACEUTICALS (IF APPLICABLE)--NA


20.00 mm
12 m
71.00 mm
MEGA We care
Rx Prescription Drug
Dapiflozin 10
Dapagliflozin Tablets 10 mg
3 x 10 Tablets
Space For Over Printing
23 x 71 mm
No Text Matter
Space For Pharma Code
2.5 mm
Artwork Code
XXXXXXXX/XX
2.5 mm
2.5 mm
Dapiflozin
Dapagliflozin Tablets 10 mg
3 x 10 Tablets
10
Space For Pharma Code 7 x 20 mm
12 mm
Each film coated tablet contains:
Dapagliflozin 10 mg
Product Specifications : Manufacturer
Indications, Dosage, Contraindications, Side Effects (see enclosed leaflet)
Keep out of reach of children
Jauhi Ubat dari Kanak Kanak
Protect from light and moisture
Store below 30°C in a dry place
Read the instructions carefully before use.
Do not exceed prescribed dose.
HARUS DENGAN RESEP DOKTER
Route of administration: Oral use only.
Controlled Medicine/ Ubat Terkawal
Mfg. Lic. No.: MH/DRUGS/25/KD/638
Manufactured for :
MEGA LIFESCIENCES (AUSTRALIA) PTY LTD
Victoria 3810, Australia.
Product Registration Holder in Malaysia:
MEGA LIFESCIENCES SDN. BHD.
B-28-02, The Ascent, Paradigm No. 1,
Jalan SS7/26A, Kelana Jaya, 47301 Petaling Jaya,
Selangor, Malaysia
In Indonesia Imported by / Di Import Oleh:
PT. MEGA LIFESCIENCES INDONESIA
Bogor - Indonesia
Manufactured by :
INVENTIA HEALTHCARE LIMITED
F1-F1/1-F75/1, Additional Ambernath M.I.D.C.,
Ambernath (East), Thane 421506,
Maharashtra State, India.
NAFDAC Reg. No.:
MM Reg. No.:
Reg. No.:
MAL XXXXXXX
TZ Reg. No. :
Reg.No. DKI xxx xxx xxx
Barcode