

Pharmacode position will be varies as per width of PI

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Rx

Package Insert

INVAFLOZIN 5

(Dapagliflozin Film Coated Tablets 5 mg)

INVAFLOZIN 10

(Dapagliflozin Film Coated Tablets 10 mg)

Description:

Invaflon 5

Yellow coloured biconvex, round shaped, film coated tablets with "120" engraved on one side and plain on another side

Invaflon 10

Yellow coloured biconvex, diamond shaped film coated tablets with "121" engraved on one side and plain on another side

Inactive ingredients:

Microcrystalline cellulose, Anhydrous lactose, Sepitrap 80, Low Substituted Hydroxypropyl Cellulose (LH-11), Colloidal silicon dioxide, Magnesium stearate, Opadry II Yellow 85F520173- (polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and Ferric oxide yellow.)

Pharmacodynamics 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. 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 diastolic function, and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight.

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, dapagliflozin has a low propensity to cause hypoglycaemia. 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. 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.

Indications:

Type 2 diabetes mellitus

It is indicated in adults aged 18 years and older with type 2 diabetes mellitus as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy

In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see section Warnings And Precautions, Pharmacodynamics for available data on different combinations).

Initial Combination

It is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin monotherapy (for example, high initial HbA_{1c} levels).

Recommended Dosage and Administration:

Type 2 diabetes mellitus

Monotherapy and add-on combination therapy
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 required to reduce the risk of hypoglycaemia (see section Interactions with other Medicaments, Adverse Effects).

Initial Combination Therapy

The recommended starting doses of dapagliflozin and metformin when used as initial combination therapy are 10 mg dapagliflozin plus 500 mg metformin once daily. Patients with inadequate glycaemic control on this dose should further have their metformin dose increased according to approved local label guidelines.

Special populations

Renal impairment

No dosage adjustment is required based on renal function.

Due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR <25 mL/min.

In patients with diabetes mellitus, the glucose lowering efficacy of dapagliflozin is reduced when the glomerular filtration rate is < 45 mL/min, and is likely absent in patients with severe renal impairment. Therefore, if GFR falls below 45 mL/min, additional glucose lowering treatment should be considered in patients with diabetes mellitus if further glycaemic control is needed (see section Warnings And Precautions, Pharmacodynamics, Pharmacokinetics).

Hepatic impairment

No dosage 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 (see section Warnings And Precautions, Pharmacodynamics).

Elderly (≥ 65 years)

No dosage adjustment is recommended based on age.

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

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

Mode of administration: Oral

Pharmacokinetics:

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 AUC₀₋₂₄ 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 Tablets 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 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 [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.

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 hemodialysis 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 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 AUCs 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.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients

Warnings And Precautions:

General

Dapagliflozin should not be used in patients with type 1 diabetes mellitus.

Renal impairment

Due to limited experience, it is not recommended to initiate treatment with dapagliflozin in patients with GFR <25 mL/min.

The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients with GFR <45 mL/min and is likely absent in patients with severe renal impairment.

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 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, 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. 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)

Postmarketing 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 ureo-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Dapagliflozin Tablets 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.

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 another SGLT2 inhibitor. 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 Tablets 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.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

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.

Interactions with other Medicaments:

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 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

Concomitant use of dapagliflozin and lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

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, 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.

Other interactions

The effects of smoking, diet, herbal products and alcohol use on the pharmacokinetics of dapagliflozin have not been studied.

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.

Adverse 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 were 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.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing 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), and not known (cannot be estimated from the available data).

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Table 1. Adverse reactions in placebo-controlled clinical studies 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 ^{d,e}	Fungal infection ^f		Necrotising fasciitis of the perineum (Fournier's Gangrene) ^g
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin) ^h		Volume depletion ⁱ , Thirst ^j	Diabetic ketoacidosis ^k (when used in type 2 diabetes mellitus)	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation ^l , Dry mouth ^m		
Skin and subcutaneous tissue disorders		Rash ⁿ			
Musculoskeletal and connective tissue disorders		Back pain ^o			
Renal and urinary disorders		Dysuria ^p , Polyuria ^q	Nocturia ^r		
Reproductive system and breast disorders			Vulvovaginal pruritus ^s , Pruritus genital ^t		
Investigations		Haematocrit increased ^u , Creatinine renal clearance decreased ^v during initial treatment ^w , Dyslipidaemia ^x	Blood creatinine increased ^y during initial treatment ^z , Blood urea increased ^{aa} , Weight decreased ^{ab}		

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 Warning and Precautions
 j Adverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical trials: rash, rash generalised, 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

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.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors including dapagliflozin.

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, initial combination with metformin, 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.

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; Warning and Precautions). 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.

Increased creatinine

Adverse drug 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 ≥ 60 ml/min/1.73 m³) 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/1.73 m³ (18.5% dapagliflozin 10 mg vs 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 44 micromoles/L (≤ 0.5 mg/dl) from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

Symptoms and Treatment of 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.

Effects on Ability to Drive and Use Machine:

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.

Preclinical Safety Data:

Not applicable

Shelf life:

36 months

Storage conditions:

Store below 30°C. Protect from light & moisture. Keep out of reach of children.

PRESENTATION:

Alu-Alu Blister of 7 Tablets.
 Box containing 28 Tablets, (4 x 7's Blisters)
 Read the instructions carefully before use.

Manufactured by:

Inventia
 Inventia Healthcare Limited
 F1-F11-F15/1, Additional Ambernath M.I.D.C.,
 Ambernath (East), Thane-421506, Maharashtra State, India

Product Registration Holder in Malaysia:

HEAL OI PHARMACEUTICALS SDN. BHD,
 74-3, Jalan Wangsa Delima 6, KLSC Wangsa Maju,
 53300 Kuala Lumpur, Malaysia.

Date of Revision of Package Insert:

26-June-2024

2011341

Product Name : Invallozin 5/10 Dapagliflozin Film Coated Tablets 5/10 mg		Packaging Material : Pack Insert (Front & Back Side)		Size : 332 x 580 mm (As per Drawing)	
Location : Ambernath		Artwork No.: 2011341		Pack Size: 4 x 7 Tablets	
Substrate : 40 GSM ITC Superfine Paper (Transparency requirement)		Any Other Requirement : Booklet to be closed with tear here adhesive tape Font Size : 7.2 Pt / Font - Times New Roman		Drawing: PGB195200369 BK M 1	
No. of Colour : 01 Black				Folding Size : 76 x 30 mm (As per Drawing)	
Version No.: 1.0		Change History : 1) CC/RDP/BD/2024/101 - New Artwork		Date: 12-09-2024	
Signature and Date					
Department	Client	Packaging Development - R&D	Regulatory Affairs	Corporate Quality	

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