For the use of Registered Medical Practitioner only

# Canagliflozin Tablets 100 mg

## Canasmart 100

**1. Generic Name**
Canagliflozin Tablets 100 mg

**2. Qualitative and Quantitative Composition**
Each film coated tablet contains:
Canagliflozin hemihydrate Equivalent to Canagliflozin .....100 mg
Excipients.....q.s.
Colors: Ferric Oxide Yellow NF & Titanium Dioxide IP

**3. Dosage Form & strength**
Film-coated tablets,
100 mg

**4. Clinical particulars**
**4.1 Therapeutic Indication**
Canagliflozin is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:
- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

**4.2 Posology and method of administration**
Posology
The recommended starting dose of Canagliflozin is 100 mg once daily. In patients tolerating Canagliflozin 100 mg once daily who have an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m2 or CrCl ≥ 60 mL/min and need tighter glycaemic control, the dose can be increased to 300 mg once daily. For dose adjustment recommendations according to eGFR.
Care should be taken when increasing the dose in patients ≥ 75 years of age, patients with known cardiovascular disease, or other patients for whom the initial Canagliflozin-induced diuresis poses a risk. In patients with evidence of volume depletion, correcting this condition prior to initiation of Canagliflozin is recommended.
When Canagliflozin is used as add-on therapy with insulin or an insulin secretagogue (e.g., sulphonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia

Method of administration
For oral use
Canagliflozin should be taken orally once a day, preferably before the first meal of the day. Tablets should be swallowed whole.
If a dose is missed, it should be taken as soon as the patient remembers; however, a double dose should not be taken on the same day.

**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 Canagliflozin for glycaemic control 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 patients with an eGFR < 60 mL/min/1.73 m2 or CrCl < 60 mL/min, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) was reported, particularly with the 300 mg dose. In addition, in such patients more events of elevated potassium and greater increases in serum creatinine and blood urea nitrogen (BUN) were reported.
Therefore, the Canagliflozin dose **should be limited to 100 mg once daily** in patients with eGFR < 60 mL/min/1.73 m2 or CrCl < 60 mL/min.
Regardless of pretreatment eGFR, patients on Canagliflozin experienced an initial fall in eGFR that thereafter attenuated over time.
Monitoring of renal function is recommended as follows:
- Prior to initiation of Canagliflozin and at least annually, thereafter.
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter.
There is experience with Canagliflozin for the treatment of diabetic kidney disease (eGFR ≥ 30 mL/min/1.73 m2) both with and without albuminuria. While both groups of patients benefitted, patients with albuminuria may benefit more from treatment with Canagliflozin.
Use in patients at risk for adverse reactions related to volume depletion
Due to its mechanism of action, Canagliflozin, by increasing urinary glucose excretion (UGE) induces an osmotic diuresis, which may reduce intravascular volume and decrease blood pressure. In controlled clinical studies of Canagliflozin, increases in adverse reactions related to volume depletion (e.g., postural dizziness, orthostatic hypotension, or hypotension) were seen more commonly with the 300 mg dose and occurred most frequently in the first three months.
Caution should be exercised in patients for whom a Canagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients with an eGFR < 60 mL/min/1.73 m2, patients on anti-hypertensive therapy with a history of hypotension, patients on diuretics, or elderly patients (≥ 65 years of age).
Due to volume depletion, generally small mean decreases in eGFR were seen within the first 6 weeks of treatment initiation with Canagliflozin. In patients susceptible to greater reductions in intravascular volume as described above, larger decreases in eGFR (> 30%) were sometimes seen, which subsequently improved, and infrequently required interruption of treatment with Canagliflozin.
Patients should be advised to report symptoms of volume depletion. Canagliflozin 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).
For patients receiving Canagliflozin, in case of intercurrent conditions that may lead to volume depletion (such as a gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including renal function tests), and serum electrolytes is recommended. Temporary interruption of treatment with Canagliflozin may be considered for patients who develop volume depletion while on Canagliflozin therapy until the condition is corrected. If interrupted, consideration should be given to more frequent glucose monitoring.

**Diabetic ketoacidosis**
Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including Canagliflozin. 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 Canagliflozin. Risk of DKA appears to be higher in patients with moderately to severely decreased renal function who require insulin.
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 Canagliflozin 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 Canagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.
Before initiating Canagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered.
Diabetic ketoacidosis may be prolonged after discontinuation of Canagliflozin in some patients, i.e. it may last longer than expected from the plasma half-life of Canagliflozin. Prolonged glucosuria has been observed along with persistent DKA. Canagliflozin-independent factors might be involved in prolonged periods of DKA. Insulin deficiency may contribute to prolonged diabetic ketoacidosis and has to be corrected when verified.
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 Canagliflozin in patients with type 1 diabetes have not been established and Canagliflozin should not be used for treatment of patients with type 1 diabetes. Limited data from clinical studies suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

**Lower limb amputations**
In long-term clinical studies of Canagliflozin in patients with type 2 diabetes with established cardiovascular disease (CVD) or at least 2 risk factors for CVD, Canagliflozin was associated with an increased risk of lower limb amputation versus placebo (0.63 vs 0.34 events per 100 patient-years, respectively), and this increase occurred primarily in the toe and midfoot (see section 4.8). In a long-term clinical study in patients with type 2 diabetes and diabetic kidney disease, no difference in lower limb amputation risk was observed in patients treated with Canagliflozin 100 mg relative to placebo. In this study precautionary measures as outlined below were applied. As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown.
Before initiating Canagliflozin, consider factors in the patient history that may increase the risk for amputation. As precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration. Consideration may also be given to stopping treatment with Canagliflozin in patients who develop events which may precede amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.

**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, Canagliflozin should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

**Elevated haematocrit**
Haematocrit increase was observed with Canagliflozin treatment; therefore, careful monitoring in patients with already elevated haematocrit is warranted.

**Elderly (≥ 65 years old)**
Elderly patients may be at a greater risk for volume depletion, are more likely to be treated with diuretics, and to have impaired renal function. In patients ≥ 75 years of age, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) was reported. In addition, in such patients greater decreases in eGFR were reported.

**Genital mycotic infections**
Consistent with the mechanism of sodium glucose co-transporter 2 (SGLT2) inhibitions with increased UGE, vulvovaginal candidiasis in females and balanitis or balanoposthitis in males were reported in clinical studies with Canagliflozin. Male and female patients with a history of genital mycotic infections were more likely to develop an infection. Balanitis or balanoposthitis occurred primarily in uncircumcised male patients which in some instances resulted in phimosis and/or circumcision. The majority of genital mycotic infections were treated with topical antifungal treatments, either prescribed by a healthcare professional or self-treated while continuing therapy with Canagliflozin.

**Urinary tract infections**
Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with Canagliflozin, frequently leading to treatment interruption. Temporary interruption of Canagliflozin should be considered in patients with complicated urinary tract infections.

**Cardiac failure**
Experience in New York Heart Association (NYHA) class III is limited, and there is no experience in clinical studies with Canagliflozin in NYHA class IV.

**Urine laboratory assessments**
Due to its mechanism of action, patients taking Canagliflozin will test positive for glucose in their urine.

**Lactose intolerance**
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.

**Sodium**
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

**4.3 Drug interactions**
**Pharmacodynamic interactions**
**Diuretics**
Canagliflozin may add to the effect of diuretics and may increase the risk of dehydration and hypotension.

**Insulin and insulin secretagogues**
Insulin and insulin secretagogues, such as sulphonylureas, can 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 canagliflozin.

**Pharmacokinetic interactions**
**Effects of other medicinal products on canagliflozin**
The metabolism of canagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyl transferase 1A9 (UGT1A9) and 2B4 (UGT2B4). Canagliflozin is transported by P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).

Enzyme inducers (such as St. John's wort [Hypericum perforatum], rifampicin, barbiturates, phenytoin, carbamazepine, ritonavir, efavirenz) may decrease the exposure to canagliflozin. Following co-administration of canagliflozin with rifampicin (an inducer of various active transporters and medicinal product- metabolising enzymes), 51% and 28% decreases in canagliflozin systemic exposure (AUC) and peak concentration (Cmax) were observed. These decreases in exposure to canagliflozin may decrease efficacy.
If a combined inducer of these UGT enzymes and transport proteins must be co-administered with canagliflozin, monitoring of glycaemic control to assess response to canagliflozin is appropriate. If an inducer of these UGT enzymes must be co-administered with canagliflozin, increasing the dose to 300 mg once daily may be considered if patients are currently tolerating canagliflozin 100 mg once daily, have an eGFR ≥ 60 mL/min/1.73 m2 or CrCl ≥ 60 mL/min, and require additional glycaemic control. In patients with an eGFR 45 mL/min/1.73 m2 to < 60 mL/min/1.73 m2 or CrCl 45 mL/min to < 60 mL/min taking canagliflozin 100 mg who are receiving concurrent therapy with a UGT enzyme inducer and who require additional glycaemic control, other glucose-lowering therapies should be considered.
Cholestyramine may potentially reduce canagliflozin exposure. Dosing of canagliflozin should occur at least 1 hour before or 4-6 hours after administration of a bile acid sequestrant to minimise possible interference with their absorption.
Interaction studies suggest that the pharmacokinetics of canagliflozin are not altered by metformin, hydrochlorothiazide, oral contraceptives (ethinyl estradiol and levonorgestrol), ciclosporin, and/or probenecid.

**Effects of canagliflozin on other medicinal products**
Digoxin
The combination of canagliflozin 300 mg once daily for 7 days with a single dose of digoxin 0.5 mg followed by 0.25 mg daily for 6 days resulted in a 20% increase in AUC and a 36% increase in Cmax of digoxin, probably due to inhibition of P-gp. Canagliflozin has been observed to inhibit P-gp in vitro. Patients taking digoxin or other cardiac glycosides (e.g., digitoxin) should be monitored appropriately.

*Lithium*
The concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more closely during treatment with canagliflozin, especially during initiation and dosage changes.

*Dabigatran*
The effect of concomitant administration of canagliflozin (a weak P-gp inhibitor) on dabigatran etexilate (a P-gp substrate) has not been studied. As dabigatran concentrations may be increased in the presence of canagliflozin, monitoring (looking for signs of bleeding or anaemia) should be exercised when dabigatran is combined with canagliflozin.

*Simvastatin*
The combination of canagliflozin 300 mg once daily for 6 days with a single dose of simvastatin (CYP3A4 substrate) 40 mg resulted in a 12% increase in AUC and a 9% increase in Cmax of simvastatin and an 18% increase in AUC and a 26% increase in Cmax of simvastatin acid. The increases in simvastatin and simvastatin acid exposures are not considered clinically relevant.
Inhibition of BCRP by canagliflozin cannot be excluded at an intestinal level and increased exposure may therefore occur for medicinal products transported by BCRP, e.g. certain statins like rosuvastatin and some anti-cancer medicinal products.
In interaction studies, canagliflozin at steady-state had no clinically relevant effect on the pharmacokinetics of metformin, oral contraceptives (ethinyl estradiol and levonorgestrol), glibenclamide, paracetamol, hydrochlorothiazide, or warfarin.

**Medicinal product/Laboratory test interference**
***1,5-AG assay***
Increases in urinary glucose excretion with Canagliflozin can falsely lower 1,5-anhydroglucitol (1,5-AG) levels and make measurements of 1,5-AG unreliable in assessing glycaemic control. Therefore, 1,5-AG assays should not be used for assessment of glycaemic control in patients on canagliflozin. For further detail, it may be advisable to contact the specific manufacturer of the 1,5-AG assay.

**4.3 Use in special populations (such as pregnant women, lactating women, Paediatric patients, geriatric patients etc.)**

**Pregnancy**
There are no data from the use of canagliflozin in pregnant women. Studies in animals have shown reproductive toxicity
Canagliflozin should not be used during pregnancy. When pregnancy is detected, treatment with canagliflozin should be discontinued.

**Breast-feeding**
It is unknown whether canagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of canagliflozin/metabolites in milk, as well as pharmacologically mediated effects in breast-feeding offspring and juvenile rats exposed to canagliflozin. A risk to newborns/infants cannot be excluded. Canagliflozin should not be used during breast-feeding.

**Fertility**
The effect of canagliflozin on fertility in humans has not been studied. No effects on fertility were observed in animal studies.

**4.7 Effects on ability to drive and use machines**
Canagliflozin has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia when canagliflozin is used as add-on therapy with insulin or an insulin secretagogue, and to the elevated risk of adverse reactions related to volume depletion, such as postural dizziness.

**4.8 Undesirable effects**
Adverse reactions in table 1 are based on the pooled analysis of the placebo- and active-controlled studies described above. Adverse reactions reported from world-wide postmarketing use of canagliflozin are also included in this tabulation. Adverse reactions listed below are classified according to frequency and system organ class. 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), not known (cannot be estimated from the available data).

**Table 1: Tabulated list of adverse reactions (MedDRA) from placebo and active-controlled studies and from postmarketing experience**

| System organ class | Adverse reaction |
|---|---|
| *Frequency* | |
| ***Infections and infestations*** | |
| Very common | Vulvovaginal candidiasis |
| Common | Balanitis or balanoposthitis, Urinary tract infection, genital mycotic infection, nasopharyngitis, upper respiratory tract infection |
| Not known | Fournier gangrene (necrotising fasciitis of the perineum [Fournier's gangrene]) |
| ***Immune system disorders*** | |
| Rare | Anaphylactic reaction |
| ***Metabolism and nutrition disorders*** | |
| Very common | Hypoglycaemia in combination with insulin or sulphonylurea, Dehydration |
| Common | Diabetic ketoacidosis |
| ***Nervous system disorders*** | |
| Uncommon | Dizziness, postural*, Syncope |
| ***Vascular disorders*** | |
| Uncommon | Hypotension, Orthostatic hypotension |
| ***Gastrointestinal disorders*** | |
| Common | Constipation, Thirst, Nausea |

| | |
|---|---|
| *Skin and subcutaneous tissue disorders* | |
| uncommon | Photosensitivity, Rash, Urticaria |
| rare | Angioedema |
| *Musculoskeletal and connective tissue disorders* | |
| uncommon | Bone fracture |
| *Renal and urinary disorders* | |
| common | Polyuria or Pollakiuria |
| uncommon | Renal failure (mainly in the context of volume depletion) |
| Investigations | |
| Common | Dyslipidaemia, Haematocrit increased |
| uncommon | Blood creatinine increased Blood urea increased, Blood potassium increased, Blood phosphate increased |
| *Surgical and medical procedures* | |
| uncommon | Lower limb amputations (mainly of the toe and midfoot) especially in patients at high risk for heart disease |

**4.9 Overdose**
Single doses up to 1,600 mg of canagliflozin in healthy subjects and canagliflozin 300 mg twice daily for 12 wekes in patients with type 2 diabetes were generally well- tolerated.

**Therapy**
In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute clinical measures if required. Canagliflozin was negligibly removed during a 4-hour haemodialysis session. Canagliflozin is not expected to be dialysable by peritoneal dialysis

**5 Pharmacological properties**
Pharmacotherapeutic group: Drugs used in diabetes, Blood glucose lowering drugs, excluding insulins. ATC code: A10BK02

**5.1 Mechanism of action**
The SGLT2 transporter, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Patients with diabetes have been shown to have elevated renal glucose reabsorption which may contribute to persistent elevated blood glucose concentrations. Canagliflozin is an orally-active inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases UGE, lowering elevated plasma glucose concentrations by this insulin-independent mechanism in patients with type 2 diabetes. The increased UGE with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect leading to a reduction in systolic blood pressure; the increase in UGE results in a loss of calories and therefore a reduction in body weight, as has been demonstrated in studies of patients with type 2 diabetes.
Canagliflozin's action to increase UGE directly lowering plasma glucose is independent of insulin. Improvement in homeostasis model assessment for beta-cell function (HOMA beta-cell) and improved beta-cell insulin secretion response to a mixed-meal challenge has been observed in clinical studies with canagliflozin.
In phase 3 studies, pre-meal administration of canagliflozin 300 mg provided a greater reduction in postprandial glucose excursion than observed with the 100 mg dose. This effect at the 300 mg dose of canagliflozin may, in part, be due to local inhibition of intestinal SGLT1 (an important intestinal glucose transporter) related to transient high concentrations of canagliflozin in the intestinal lumen prior to medicinal product absorption (canagliflozin is a low potency inhibitor of the SGLT1 transporter). Studies have shown no glucose malabsorption with canagliflozin.
Canagliflozin increases the delivery of sodium to the distal tubule by blocking SGLT2-dependent glucose and sodium reabsorption thereby increasing tubuloglomerular feedback, which is associated with a reduction in intraglomerular pressure and a decrease in hyperfiltration in preclinical models of diabetes and clinical studies.

**5.2 Pharmacodynamic properties**
Following single and multiple oral doses of canagliflozin to patients with type 2 diabetes, dose-dependent decreases in RTG and increases in UGE were observed. From a starting value of RTG of approximately 13 mmol/L, maximal suppression of 24-hour mean RTG was seen with the 300 mg daily dose to approximately 4 mmol/L to 5 mmol/L in patients with type 2 diabetes in phase 1 studies, suggesting a low risk for treatment-induced hypoglycaemia. The reductions in RT led to increased UGE in subjects with type 2 diabetes treated with either 100 mg or 300 mg of canagliflozin ranging from 77 g/day to 119 g/day across the phase 1 studies; the UGE observed translates to a loss of 308 kcal/day to 476 kcal/day. The reductions in RTG and increases in UGE were sustained over a 26-week dosing period in patients with type 2 diabetes. Moderate increases (generally < 400 mL to 500 mL) in daily urine volume were seen that attenuated over several days of dosing. Urinary uric acid excretion was transiently increased by canagliflozin (increased by 19% compared to baseline on day 1 and then attenuating to 6% on day 2 and 1% on day 13). This was accompanied by a sustained reduction in serum uric acid concentration of approximately 20%.
In a single-dose study in patients with type 2 diabetes, treatment with 300 mg before a mixed meal delayed intestinal glucose absorption and reduced postprandial glucose through both a renal and a non-renal mechanism.

**5.3 Pharmacokinetic properties**
Absorption
The mean absolute oral bioavailability of canagliflozin is approximately 65%. Co-administration of a high-fat meal with canagliflozin had no effect on the pharmacokinetics of canagliflozin; therefore, Canagliflozin may be taken with or without food. However, based on the potential to reduce postprandial plasma glucose excursions due to delayed intestinal glucose absorption, it is recommended that Canagliflozin be taken before the first meal of the day.

Distribution
The mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects was 83 5 litres, suggesting extensive tissue distribution. Canagliflozin is extensively bound to proteins in plasma (99%), mainly to albumin. Protein binding is independent of canagliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

Biotransformation
O-glucuronidation is the major metabolic elimination pathway for canagliflozin, which is mainly glucuronidated by UGT1A9 and UGT2B4 to two inactive O-glucuronide metabolites. CYP3A4-mediated (oxidative) metabolism of canagliflozin is minimal (approximately 7%) in humans.

In in vitro studies, canagliflozin neither inhibited cytochrome P450 CYP1A2, CYP2A6, CYP2C19, CYP2D6, or CYP2E1, CYP2B6, CYP2C8, CYP2C9, nor induced CYP1A2, CYP2C19, CYP2B6, CYP3A4 at higher than therapeutic concentrations. No clinically relevant effect on CYP3A4 was observed in vivo

Elimination
Following administration of a single oral [14C] canagliflozin dose to healthy subjects, 41.5%, 7.0%, and 3.2% of the administered radioactive dose was recovered in faeces as canagliflozin, a hydroxylated metabolite, and an O-glucuronide metabolite, respectively. Enterohepatic circulation of canagliflozin was negligible.

Approximately 33% of the administered radioactive dose was excreted in urine, mainly as O-glucuronide metabolites (30.5%). Less than 1% of the dose was excreted as unchanged canagliflozin in urine. Renal clearance of canagliflozin 100 mg and 300 mg doses ranged from 1.30 mL/min to 1.55 mL/min.
Canagliflozin is a low-clearance substance, with a mean systemic clearance of approximately 192 mL/min in healthy subjects following intravenous administration.

Renal impairment
A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using CrCl based on the Cockroft-Gault equation) compared to healthy subjects. The study included 8 subjects with normal renal function (CrCl ≥ 80 mL/min), 8 subjects with mild renal impairment (CrCl 50 mL/min to < 80 mL/min), 8 subjects with moderate renal impairment (CrCl 30 mL/min to < 50 mL/min), and 8 subjects with severe renal impairment (CrCl < 30 mL/min) as well as 8 subjects with ESKD on haemodialysis.
The Cmax of canagliflozin was moderately increased by 13%, 29%, and 29% in subjects with mild, moderate, and severe renal failure, respectively, but not in subjects on haemodialysis. Compared to healthy subjects, plasma AUC of canagliflozin was increased by approximately 17%, 63%, and 50% in subjects with mild, moderate, and severe renal impairment, respectively, but was similar for ESKD subjects and healthy subjects.
Canagliflozin was negligibly removed by haemodialysis.

Hepatic impairment
Relative to subjects with normal hepatic function, the geometric mean ratios for Cmax and AUC∞ of canagliflozin were 107% and 110%, respectively, in subjects with Child-Pugh class A (mild hepatic impairment) and 96% and 111%, respectively, in subjects with Child-Pugh class B (moderate) hepatic impairment following administration of a single 300 mg dose of canagliflozin. These differences are not considered to be clinically meaningful. There is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment.
Elderly (≥ 65 years old)

Age had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis.

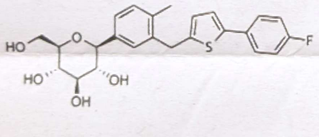
Paediatric population
A paediatric phase 1 study examined the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents ≥ 10 to < 18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.
Pharmacogenetics
Both UGT1A9 and UGT2B4 are subject to genetic polymorphism. In a pooled analysis of clinical data, increases in canagliflozin AUC of 26% were observed in UGT1A9*1/*3 carriers and 18% in UGT2B4*2/*2 carriers. These increases in canagliflozin exposure are not expected to be clinically relevant. The effect of being homozygote (UGT1A9*3/*3, frequency < 0.1%) is probably more marked, but has not been investigated.
Gender, race/ethnicity, or body mass index had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis.

**6 Nonclinical properties**
**6.1 Animal toxicology or pharmacology**
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.
Canagliflozin showed no effects on fertility and early embryonic development in the rat at exposures up to 19 times the human exposure at the maximum recommended human dose (MRHD).

In an embryo-foetal development study in rats, ossification delays of metatarsal bones were observed at systemic exposures 73 times and 19 times higher than the clinical exposures at the 100 mg and 300 mg doses. It is unknown whether ossification delays can be attributed to effects of canagliflozin on calcium homeostasis observed in adult rats. Ossification delays were also observed for the combination of canagliflozin and metformin, which were more prominent than for metformin alone at canagliflozin exposures 43 times and 12 times higher than clinical exposures at 100 mg and 300 mg doses.
In a pre- and postnatal development study, canagliflozin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring at maternally toxic doses > 30 mg/kg/day (exposures ≥ 5.9 times the human exposure to canagliflozin at the MHRD). Maternal toxicity was limited to decreased body weight gain.

A study in juvenile rats administered canagliflozin from day 1 through day 90 postnatal did not show increased sensitivity compared to effects observed in adults rats. However, dilatation of the renal pelvis was noticed with a No Observed Effect Level (NOEL) at exposures 2.4 times and 0.6 times the clinical exposures at 100 mg and 300 mg doses, respectively, and did not fully reverse within the approximately 1-month recovery period. Persistent renal findings in juvenile rats can most likely be attributed to reduced ability of the developing rat kidney to handle canagliflozin-increased urine volumes, as functional maturation of the rat kidney continues through 6 weeks of age.
Canagliflozin did not increase the incidence of tumours in male and female mice in a 2-year study at doses of 10, 30, and 100 mg/kg. The highest dose of 100 mg/kg provided up to 14 times the clinical dose of 300 mg based on AUC exposure. Canagliflozin increased the incidence of testicular Leydig cell tumours in male rats at all doses tested (10, 30, and 100 mg/kg); the lowest dose of 10 mg/kg is approximately 1.5 times the clinical dose of 300 mg based on AUC exposure. The higher doses of canagliflozin (100 mg/kg) in male and female rats increased the incidence of pheochromocytomas and renal tubular tumours. Based on AUC exposure, the NOEL of 30 mg/kg/day for pheochromocytomas and renal tubular tumours is approximately 4.5 times the exposure at the daily clinical dose of 300 mg. Based on preclinical and clinical mechanistic studies, Leydig cell tumours, renal tubule tumours, and pheochromocytomas are considered to be rat-specific. Canagliflozin-induced renal tubule tumours and pheochromocytomas in rats appear to be caused by carbohydrate malabsorption as a consequence of intestinal SGLT1 inhibitory activity of canagliflozin in the gut of rats; mechanistic clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the maximum recommended clinical dose. The Leydig cell tumours are associated with an increase in luteinizing hormone (LH), which is a known mechanism of Leydig cell tumour formation in rats. In a 12-week clinical study, unstimulated LH did not increase in male patients treated with canagliflozin.

**7 Description**
Canagliflozin is a C-glycosyl compound that is used (in its hemihydrate form) for treatment of type II diabetes via inhibition of sodium-glucose transport protein subtype 2. It has a role as a hypoglycemic agent and a sodium-glucose transport protein subtype 2 inhibitor. It is a C-glycosyl compound, a member of thiophenes and an organofluorine compound. The chemical name for Canagliflozin is (2S,3R,4R,5S,6R)-2-[3-[[5-(4-fluorophenyl)thiophen-2-yl]methyl]-4-methylphenyl]-6-(hydroxymethyl)oxane-3,4,5-triol. Its empirical formula is C24H25FO5S
The molecular weight of Canagliflozin is 444.5 g/mol.
The structural formula is:




**8 Pharmaceutical particulars**
**8.1 Incompatibilities**
Not applicable.

**8.2 Shelf- Life**
24 months

**8.2 Packaging information**
Alu-PVC/PVDC blister pack

**8.4 Storage and handling instructions**
Store at a temperature not exceeding 30°C, Protect from light & moisture.

**9 PATIENT COUNSELING INFORMATION**
**1) What is the use of Canagliflozin Tablets?**
Canagliflozin Tablet is a type of medicine known as a sodium-glucose cotransporter-2 (SGLT2) inhibitor used for the treatment of type -2 diabetes. It lowers blood sugar levels by blocking the action of SGLT-2 in the kidney and removing excess sugar from your body through urination.

**2) Can you stop treatment when you feel OK:**
No, do not stop the treatment course even if you feel better. Continue taking this medicine and complete the prescribed course for the best effects.

**3) Warnings and precautions:**
Canagliflozin Tablet should not be used in patients with type 1 diabetes or diabetic ketoacidosis. Before you start taking Canagliflozin Tablet , tell your doctor if you have serious heart disease or if you have had a stroke, low blood pressure (hypotension), and severe liver or kidney disease. Canagliflozin Tablet, when used with insulin, may lower the blood sugar level, leading to hypoglycemia, which can be fatal. Your doctor may adjust the dose by lowering the dose of insulin or Canagliflozin Tablet in this case. If you experience rapid weight loss, feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, talk to a doctor or go to the nearest hospital immediately.

**4) How should I take Canagliflozin Tablets?**
Swallow the tablet whole with some water.

**5) If you have taken too many tablets?**
Contact your doctor immediately or go to the nearest hospital casualty department taking any remaining medication and this patient information leaflet with you.

**6) If you forget to take Canagliflozin Tablets?**
If you miss a dose of Canagliflozin Tablets, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule. Do not double the dose.

**10 Detail of product permission or license number**
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