CANAGLU® 100 mg

Canagliflozin hydrate

Mitsubishi Tanabe Pharma

Summary of Product Characteristic

1. NAME OF THE MEDICINE PRODUCT

CANAGLU® 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

(INN: canagliflozin)

CANAGLU® 100 mg

Each tablet contains 102 mg canagliflozin hydrate equivalent to 100 mg of canagliflozin

3. PHARMACEUTICAL FORM

Tablets are Light-yellow, Film-coated and round-shaped. Tablet size and weight are as follows: Diameter 7.6 mm, Thickness 3.4 mm, Weight 144.3 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Monotherapy:
CANAGLU® is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

Combination therapy:
CANAGLU® is indicated in patient with type 2 diabetes mellitus to improve glycemic control in combination with metformin, sulfonylureas, PPAR agonist (e.g., thiazolidinediones), rapid insulin secretagogues, alpha-glucosidase inhibitors, or dipeptidyl peptidase-4 inhibitors when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

4.2 Posology and method of administration

The usual adult dosage for oral use is 100 mg of canagliflozin administered orally once daily either before or after breakfast.

4.3 Contraindications

CANAGLU® is contraindicated in the following patients.

1) Patients with a history of hypersensitivity to any of the ingredients of this product
2) Patients with severe ketosis, diabetic coma or pre-coma. [Treatment with this product is not appropriate because such patients require rapid correction of hyper-glycaemia with transfusion and insulin.]
3) Patients with severe infection, pre- or post-operative patients, and patients with serious traumatic injury [Treatment with this product is not appropriate because glycemic control with insulin injection is desirable in such patients.]

4.4 Special warnings and precautions for use

Careful Administration

CANAGLU® should be administered with care in the following patients.

1) This product should be administered only to patients diagnosed with type 2 diabetes mellitus, not to patients with type 1 diabetes mellitus.
2) Patient with renal impairment
   - Patients with severe renal impairment or patients with end stage renal failure undergoing dialysis [This product should not be administered since its effect cannot be expected in these patients. (See "Important Precautions" of this section, section 5.2)]
   - Patient with moderate renal impairment [The necessity of treatment with this product should be carefully considered since the drug may be insufficiently effective. (See "Important Precautions" of this section, sections 5.1 and 5.2)]
3) Patients with cardiac failure (NYHA class IV) [There has been no clinical experience establishing its safety in such patients.]
4) The following patients or conditions [Hypoglycaemia may occur.]
   - Pituitary insufficiency or adrenal insufficiency
   - Malnutrition, starvation, irregular diet, insufficient dietary intake or debility
   - Extreme muscle exercise
   - Patients with excessive alcohol intake
5) Patients prone to developing dehydration (such as patients having extremely poor glycemic control, elderly patients, patients using concomitant diuretics) [The diuretic action of this product may cause dehydration. (See "Important Precautions" of this section, sections 4.5 and 4.8)]
6) Patients with urinary tract infection or genital infection [Symptoms may be aggravated. (See "Important Precautions" of this section and section 4.8)]
7) Patients with Severe Hepatic Impairment [There have been no clinical studies in these subjects (Child-Pugh total score of >9). (See section 5.2)]

Important Precautions

1) Prior to the use of this product, patients should be instructed to recognize hypoglycemic symptoms and their management. In particular, when used in combination with insulin, sulfonylurea or rapid-acting insulin secretagogues, this product may increase the risk of hypoglycaemia. In order to decrease the risk of hypoglycaemia, a reduction in the dose of insulin, sulfonylurea or rapid-acting insulin secretagogues should be considered. (see "Careful Administration" of this section, sections 4.5 and 4.8)
2) Use of this product should be considered only when there is inadequate response to diet and exercise therapy, which are fundamental for treatment of diabetes mellitus, after adequate trial of the therapies.
3) During treatment with this product, blood glucose should be regularly monitored, and the effect of the drug should be checked. If the response to this product is inadequate after 3 months of treatment, a change to other treatment should be considered.
4) The diuretic action of this product may cause polyuria or pollakiuria. Since intravascular volume may decrease, patients should be carefully observed and instructed to drink an adequate amount of fluids. In particular, patients prone to developing decreased intravascular volume (such as elderly patients, patients with renal impairment, patients using concomitant diuretics) should be carefully monitored for the occurrence of dehydration, diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, cerebral infarction and other thromboembolic diseases. (See "Careful Administration" and "Use in the Elderly" of this section, sections 4.5 and 4.8)
5) Urinary tract infection or genital infection, which leads to serious infections such as pyelonephritis, vulval or perineal necrotising fasciitis (Fournier's gangrene), and sepsis, may occur. Patients should be adequately monitored for the occurrence of urinary tract infection or genital infection. If these infections are observed, appropriate therapeutic measures should be taken and discontinuation of this product should be considered according to the patient's

condition. Patients should be instructed to recognize symptoms of urinary tract infection and genital infection and their management. (See "Careful Administration" of this section and section 4.8)

6) Since this product may cause increased serum creatinine or decreased estimated glomerular filtration rate (eGFR), renal function should be regularly monitored during treatment with this product. The course of patients with renal impairment should be adequately observed, and discontinuation of administration should be considered if eGFR is continuously less than 45 mL/min/1.73 m^2. (See "Careful Administration" of this section)
7) Acceleration of urinary glucose excretion as a mechanism of action of this product may induce hypermetabolism of fatty acid and ketosis even if blood glucose is well controlled, which leads to ketoacidosis. Since the symptoms may occur without remarkable hyperglycemia, caution should be exercised in the following points:
   - Preform laboratory tests including blood or urine ketone bodies measurements if the patient develops nausea/vomiting, decreased appetite, abdominal pain, excessive thirst, malaise, dyspnea, disturbed consciousness, or similar conditions. Discontinue this product and take appropriate actions if the tests reveal any abnormalities.
   - In particular, ketoacidosis is likely to occur in patients having symptoms accompanied by reduced insulin secretion, reduction or discontinuation of insulin preparations, excessive restriction of carbohydrate intake, insufficient dietary intake, infections, or dehydration. Such patients should be adequately monitored.
   - Patients should be instructed to:
     - recognize symptoms of ketoacidosis (nausea/vomiting, decreased appetite, abdominal pain, excessive thirst, malaise, dyspnea, disturbed consciousness).
     - consult with their doctor immediately if these symptoms are observed.
     - recognize that ketoacidosis may occur even if the blood glucose level is not high.
8) Priority should be given to treatment of dysuria, anuria, oliguria, or urinary retention if patients present with these symptoms. In such cases, treatment with other drugs should be considered.
9) Since decreased weight has been reported with administration of this product, caution should be exercised to excessive weight loss.

Use in the Elderly

Since elderly patients often have reduced physiological function and may be slow to recognize signs of dehydration (such as thirst) (See "Important Precautions" of this section and section 4.8), this product should be administered carefully with close monitoring of the patient's condition.

Pediatric Use

No clinical study was conducted for pediatric use.

Precaution concerning Use

<Precautions Concerning the Preparation of the Drug >
For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the PTP sheet prior to use. If the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.

Other Precautions

In the integrated analysis of results from two large-scale clinical studies of canagliflozin conducted outside Japan in type 2 diabetes mellitus patients with poor glycemic control and a history of or risk factors for cerebrovascular/cardiovascular disease, the frequency of lower-limb amputation in canagliflozin (100 mg or 300 mg once daily dosage regimen)-treated patients was statistically higher compared with that in placebo-treated patients (hazard ratio: 1.97; 95% confidence interval: 1.41–2.75).
The approved dosage and administration for CANAGLU® is 100 mg/day.

4.5 Interactions with other medicinal products and other forms of interactions

This product is primarily metabolized by UGT1A9 and UGT2B4. Canagliflozin is a substrate of P-glycoprotein, multidrug resistance-associated protein 2 and breast cancer resistance protein. Canagliflozin weakly inhibits P-glycoprotein and multidrug resistance-associated protein 2. (See section 5.2)

Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs for diabetes mellitus Sulfonylurea Rapid-acting insulin secretagogues α-glucosidase inhibitors Biguanide Thiazolidine DPP-4 inhibitors GLP-1 receptor agonists Insulin, etc. (see section 4.8)	Hypoglycemic symptoms may occur. In particular, since the risk of hypoglycaemia may be increased when used in combination with insulin, sulfonylurea or rapid-acting insulin secretagogues, a reduction in the dose of these drugs should be considered.	Antihyperglycaemic action is intensified.
Drugs that intensify antihyperglycemic action β-blockers Salicylic acid Monoamine oxidase inhibitors, etc.	When this product is co-administered, blood glucose level and patient's other conditions should be carefully observed.	Antihyperglycaemic action is intensified.
Drugs that reduce antihyperglycemic action Adrenaline Adrenal cortex hormones Thyroid hormones, etc.	When this product is co-administered, blood glucose level and patient's other conditions should be carefully observed.	Antihyperglycaemic action is reduced.
Digoxin (See section 5.2)	It has been reported that C_{max} and AUC of digoxin were increased by 36% and 20%, respectively when the drug was co-administered with canagliflozin 300 mg. Patients should be therefore appropriately monitored.	P-glycoprotein is inhibited by canagliflozin.
Rifampicin, Phenytoin, Phenobarbital, Ritonavir, etc. (See section 5.2)	It has been reported that C_{max} and AUC of canagliflozin were decreased by 28% and 51%, respectively when this product was co-administered with rifampicin. Patients should be therefore appropriately monitored.	The metabolism of canagliflozin is accelerated by the induction effect of these drugs on UGT1A9 and UGT2B4, which are metabolic enzymes for canagliflozin.
Drugs with diuretic effect Loop diuretics Thiazide diuretics, etc. (See section 4.4 and 4.8)	Caution should be exercised by adjusting diuretics dosages as needed, etc.	The diuretic effect may be intensified when canagliflozin is co-administered with these drugs.

4.6 Fertility Pregnancy and Lactation

1) Insulin, etc. must be used in pregnant women or women who may possibly be pregnant instead of this product. In a rat study, this product is transferred to the fetus and fetal exposure in the period equivalent to mid- to late- term pregnancy in humans resulted in dilated renal pelvis and renal tubules of the juvenile animals.
2) Use of this product is not recommended while breastfeeding. This product was secreted in the milk of lactating rats. Reduced body weight gain and dilated renal pelvis and renal tubules of in the offspring were observed during the lactation period.

4.7 Effects on ability to drive and use machines

Since hypoglycemic symptoms may occur, attention should be paid to patients engaged in work at altitude or driving a car, etc. (See section 4.8.)

4.8 Undesirable effects

Since the following adverse reactions may occur, patients should be adequately monitored. If abnormalities are observed, administration of this product should be discontinued and appropriate therapeutic measures should be taken.

Clinically Significant Adverse Reactions

1) Hypoglycaemia (2.7–14.1%):
   Hypoglycaemia may occur. If hypoglycemic symptoms are observed, appropriate therapeutic measures, such as intake of carbohydrate-containing food, should be taken. When this product is co-administered with an α-glucosidase inhibitor, glucose should be administered (See sections 4.4, 4.5 and 5.1).
2) Dehydration (0.1%):
   If symptoms such as thirst, polyuria, pollakiuria, decreased blood pressure are observed and dehydration is suspected, appropriate therapeutic measures such as discontinuation of this product or fluid replacement should be taken. It has been reported that dehydration led to thromboembolic diseases including cerebral infarction (See sections 4.4 and 4.5).
3) Ketoacidosis (incidence unknown):
   Ketoacidosis including diabetic ketoacidosis may occur (See section 4.4).
4) Pyelonephritis (0.1%), vulval or perineal necrotising fasciitis (Fournier's gangrene) (incidence unknown), sepsis (incidence unknown):
   Pyelonephritis or vulval or perineal necrotising fasciitis (Fournier's gangrene), which leads to sepsis including septic shock, may occur (See section 4.4).

Other Adverse Reactions

	≥1%	1%> ≥0.1%	Incidence unknown
Psychiatric/ neurological		Dizziness, postural dizziness, headache	Syncope
Gastrointestinal	Constipation, thirst	Periodontitis, abdominal distension, upper abdominal pain, diarrhoea, gastritis, gastrooesophageal reflux disease, nausea	
Cardiovascular		Tachycardia, ventricular extrasystoles, orthostatic hypotension	Hypotension
Haematological		Leukocytosis, polycythemia	
Urinary system	Cystitis, pollakiuria	Urinary tract infection, hypertonic bladder, nocturia, polyuria	
Dermatological		Contact dermatitis, eczema, pruritus, rash, urticaria, toxic skin eruption	
Eyes		Conjunctivitis	

	≥1%	1%> ≥0.1%	Incidence unknown
Ears		Vertigo, sudden hearing loss	
Reproductive system	Vulvovaginal candidiasis	Genital candidiasis, vaginal infection, vulvitis, balanitis, balanoposthitis, benign prostatic hyperplasia, genital pruritus, vulvovaginal pruritus	
Metabolic disorders	Ketosis, asymptomatic hypoglycaemia		
Investigations	Increased blood ketone body	Increased blood creatinine, increased blood potassium, increased haematocrit, blood urine present, increased red blood cell count, increased urine albumin/creatinine ratio, urine ketone body present, increased urine output	
General disorders		Asthenia, chest discomfort, hunger, malaise	
Musculoskeletal		Back pain	
Others		Weight decreased	

4.9 Overdose

Therapeutic Measures
It has been reported that, in the end-stage renal failure, nearly no canagliflozin was eliminated by 4 hours of dialysis. (See section 5.2)

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action
Sodium-glucose co-transporter 2 (SGLT2) is exclusively expressed in the proximal tubules of the kidneys, and plays a role in the reabsorption of the majority of glucose from the glomerular filtrate to the blood. Canagliflozin lowers blood glucose levels by selectively inhibiting SGLT2, thereby reducing renal glucose reabsorption and increasing urinary excretion of excess blood glucose.

SGLT2 Inhibitory Effect
Canagliflozin selectively inhibits human SGLT2 (IC_{50}: 4.2 nmol/L) (*in vitro*).

Renal Glucose Reabsorption Inhibitory Effect
In the Zucker Diabetic Fatty (ZDF) rat model of type 2 diabetes mellitus, a single oral dose of canagliflozin increased the inhibition rate of renal glucose reabsorption* and the amount of glucose excreted in urine. In patients with type 2 diabetes mellitus, a single oral dose of canagliflozin 100 mg increased the inhibition rate of renal glucose reabsorption and the urinary glucose excretion.
*Inhibition rate of renal glucose reabsorption (i.e., the difference between amount of glomerular filtrated glucose and amount of glucose excreted in urine) compared to the vehicle group.

Glucose Metabolism-improving Effect
In the ZDF rats, a single oral dose of canagliflozin lowered blood glucose levels.
In the same model, repeated oral doses of canagliflozin for 4 weeks lowered HbA1c. Multiple doses of canagliflozin suppressed elevation of blood glucose levels during oral glucose tolerance test.
In patients with type 2 diabetes mellitus, repeated oral doses of canagliflozin 100 mg once daily for 24 weeks led to a decrease in HbA1c and improved postprandial hyperglycemia.

Clinical efficacy

Monotherapy

1) Placebo-controlled, double-blind comparative study (confirmatory study)
Patients with type 2 diabetes mellitus not achieving adequate glycemic control through diet and exercise therapy (271 patients) received 100 mg, 200 mg as canagliflozin or placebo once daily for 24 weeks. The results are shown in the following table. Percent change in body weight from baseline at Week 24 (adjusted mean percent change ± standard error (SE)) was -0.76 ± 0.35% in the placebo group (93 patients) and -3.76 ± 0.35% in the canagliflozin 100 mg group (90 patients).
The incidence of hypoglycaemia as related adverse reactions to study drug was 1.1% (1/93 patients) in the placebo group and 1.1% (1/90 patients) in the canagliflozin 100 mg group.

Table: Results of a placebo-controlled double-blind comparative study (at Week 24)

	Placebo n = 93		Canagliflozin 100 mg n = 90		
	Baseline	Change from baseline	Baseline	Change from baseline	Difference in change vs. Placebo
HbA1c (%)	8.04 ± 0.70	0.29 ± 0.07	7.98 ± 0.73	-0.74 ± 0.07	-1.03 ± 0.10[♯] [-1.23, -0.83]
Fasting plasma glucose (mg/dL)	163.0 ± 32.6	3.7 ± 2.7	157.7 ± 35.7	-31.6 ± 2.8	-35.3 ± 3.9[♯] [-43.0, -27.6]
Plasma glucose 2 hours after glucose load (mg/dL)	303.0 ± 66.4	-0.5 ± 5.8	311.7 ± 72.4	-84.9 ± 5.4	-84.4 ± 8.0[♯] [-100.1, -68.7]

Baseline values are presented as mean ± SD. Change from baseline and difference in change vs. placebo are presented as adjusted mean change ± SE and difference. [♯]p<0.001. [ ]: two-sided 95% CI. HbA1c values are in NGSP units.

2) Phase 3 study in Japan (Long-term study)
Patients with type 2 diabetes mellitus not achieving adequate glycemic control through diet and exercise therapy (379 patients) received 100 mg or 200 mg as canagliflozin once daily for 52 weeks. The results are shown in the following table. Percent change in body weight from baseline (mean ± SD) was −4.42 ± 3.06% in the canagliflozin 100 mg group (127 patients).
The incidence of hypoglycaemia as an adverse reaction was 3.9% (5/127 patients).

Table: Results of a long-term study (at Week 52)

	Canagliflozin 100 mg n = 127	
	Baseline	Change from baseline
HbA1c (%)	7.84 ± 0.71	-0.80 ± 0.70 [-0.92, -0.67]

Mean ± SD, [ ]: two-sided 95% CI, HbA1c values are in NGSP units.

The results by renal function are shown in the following table.

Table: Results from long-term administration by renal function (at Week 52)

		Canagliflozin 100 mg		
		Normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2) n = 42	Mild renal impairment (eGFR: ≥ 60 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2) n = 77	Moderate renal impairment (eGFR: ≥ 45 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2) n = 8
HbA1c (%)	Baseline	8.01 ± 0.69	7.73 ± 0.73	7.96 ± 0.37
	Change from baseline	-1.02 ± 0.62 [-1.21, -0.83]	-0.68 ± 0.74 [-0.85, -0.51]	-0.74 ± 0.26 [-0.95, -0.52]

Mean ± SD, [ ]: two-sided 95% CI, HbA1c values are in NGSP units.

Combination therapy with other hypoglycemic agents

1) Combination therapy with other oral hypoglycemic agent (Phase 3 studies in Japan: long-term treatment studies)
Patients with type 2 diabetes mellitus with inadequate glycemic control on oral hypoglycemic medication in addition to diet and exercise therapy (918 patients) received 100 mg or 200 mg as canagliflozin once daily for 52 weeks. The results are shown in the following table.
The incidence of hypoglycaemia as an adverse reaction was 16.1% (20/124 patients) in combination with sulfonylureas, 4.6% (3/65 patients) in combination with rapid-acting insulin secretagogues, 0.0% (0/62 patients) in combination with α-glucosidase inhibitors, 5.6% (4/72 patients) in combination with biguanides, 4.8% (3/63 patients) in combination with thiazolidines, and 2.8% (2/71 patients) in combination with DPP-4 inhibitors.

Table: Results of a long-term study (at Week 52)

Concomitant drug		Canagliflozin 100 mg	
HbA1c (%)	Sulfonylureas	n	124
		Baseline	8.18 ± 0.99
		Change from baseline	-0.96 ± 0.69 [-1.08, -0.84]
	Rapid-acting insulin secretagogue	n	n = 65
		Baseline	8.25 ± 0.91
		Change from baseline	-1.06 ± 1.01 [-1.31, -0.81]
	α-glucosidase inhibitors	n	n = 62
		Baseline	8.02 ± 0.84
		Change from baseline	-0.91 ± 0.81 [-1.11, -0.70]
	Biguanides	n	n = 72
		Baseline	7.87 ± 0.75
		Change from baseline	-0.87 ± 0.63 [-1.02, -0.73]
	Thiazolidines	n	63
		Baseline	8.10 ± 1.04
		Change from baseline	-1.04 ± 0.88 [-1.26, -0.82]
	DPP-4 inhibitors	n	71
		Baseline	8.19 ± 0.85
		Change from baseline	-1.04 ± 0.76 [-1.22, -0.86]

Mean ± SD, [ ]: two-sided 95% CI, HbA1c values are in NGSP units.

The results by renal function are shown in the following table.

Table: HbA1c (%) from long-term administration by renal function (at Week 52)

HbA1c (%)		Canagliflozin 100 mg		
		Normal renal function (eGFR: ≥ 90 mL/min/1.73 m^2)	Mild renal impairment (eGFR: ≥ 60 mL/min/1.73 m^2 and < 90 mL/min/1.73 m^2)	Moderate renal impairment (eGFR: ≥ 45 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2)
Any concomitant drug	n	158	279	20
	Baseline	8.31 ± 0.96	8.01 ± 0.87	7.87 ± 0.91
	Change from baseline	-1.08 ± 0.95 [-1.23, -0.93]	-0.93 ± 0.67 [-1.01, -0.85]	-0.76 ± 0.89 [-1.17, -0.34]
By concomitant drug				
Sulfonylureas	n	23	98	3
	Baseline	8.12 ± 0.92	8.19 ± 1.01	8.17 ± 1.32
	Change from baseline	-0.86 ± 0.85 [-1.22, -0.49]	-0.98 ± 0.65 [-1.11, -0.85]	-1.00 ± 0.92 [-3.28, 1.28]
Rapid-acting insulin secretagogue	n	34	26	3
	Baseline	8.41 ± 0.95	8.11 ± 0.78	7.92 ± 1.20
	Change from baseline	-1.10 ± 1.20 [-1.51, -0.68]	-1.02 ± 0.64 [-1.28, -0.76]	-1.00 ± 1.37 [-2.71, 0.71]
α-glucosidase inhibitors	n	22	36	4
	Baseline	8.24 ± 0.97	7.94 ± 0.76	7.55 ± 0.64
	Change from baseline	-1.02 ± 0.77 [-1.36, -0.68]	-0.91 ± 0.82 [-1.19, -0.64]	-0.25 ± 0.82 [-1.55, 1.05]
Biguanides	n	30	40	2
	Baseline	8.17 ± 0.78	7.61 ± 0.59	8.65 ± 1.34
	Change from baseline	-1.02 ± 0.65 [-1.26, -0.77]	-0.78 ± 0.61 [-0.97, -0.58]	-0.65 ± 0.64 [-6.37, 5.07]
Thiazolidines	n	21	39	3
	Baseline	8.53 ± 1.27	7.93 ± 0.85	7.27 ± 0.32
	Change from baseline	-1.27 ± 1.15 [-1.79, -0.74]	-0.94 ± 0.71 [-1.17, -0.71]	-0.70 ± 0.30 [-1.45, 0.05]
DPP-4 inhibitors	n	28	40	3
	Baseline	8.36 ± 0.92	8.09 ± 0.81	7.97 ± 0.32
	Change from baseline	-1.21 ± 0.93 [-1.57, -0.85]	-0.92 ± 0.60 [-1.11, -0.73]	-0.90 ± 0.87 [-3.05, 1.25]

Mean ± SD, [ ]: two-sided 95% CI, HbA1c values are in NGSP units.

2) Combination therapy with insulin (Post-marketing clinical study: placebo-controlled, double-blind study and long-term extension study)
Type 2 diabetes mellitus patients achieving poor glycemic control with insulin (one formulation of mixed-, intermediate-, or long-acting type, combination with one formulation of rapid- or short-acting type was also available, the daily dose was 8 units or more and 60 units or less) in addition with diet therapy and exercise therapy (146 patients) received 100 mg as canagliflozin or placebo once daily for 16 weeks. The results are shown in the following table.
The incidences of hypoglycemic adverse drug reactions were 15.5% (11/71 patients) in the placebo group and 18.7% (14/75 patients) in the canagliflozin 100 mg group.

Table: Results of the insulin combined double-blind, placebo-controlled study (at week 16)

	Placebo n = 70		Canagliflozin 100 mg n = 76		Difference in change vs. Placebo
HbA1c (%)	Baseline	Change from baseline	Baseline	Change from baseline	-1.10 ± 0.11[#] [-1.33, -0.87]
	8.85 ± 0.84	0.13 ± 0.08	8.89 ± 0.81	-0.97 ± 0.08	

Baseline values are presented as mean ± SD. Change from baseline and difference in change vs. placebo are presented as adjusted mean change ± SE and difference (Canagliflozin minus Placebo) between the changes ± SE, respectively. [#]p < 0.001, [ ]: two-sided 95% CI, HbA1c values are in NGSP units.

In the long-term extension study, patients received 100 mg as canagliflozin continuously for a maximum of 52 weeks. The change (mean ± SD) of HbA1c (NGSP) from baseline at Week 52 of the canagliflozin group (76 patients) in the double-blind comparative test was -0.88 ± 0.86%.
The incidence of adverse drug reactions of hypoglycaemia was 29.3% (22/75 patients).

3) Combination therapy with GLP-1 receptor agonist (Post-marketing clinical study: long-term treatment study)
Type 2 diabetes mellitus patients with eGFR ≥45 mL/min/1.73m^2 achieving poor glycemic control with GLP-1 agonist (liraglutide) in addition to diet therapy and exercise therapy (71 patients) received canagliflozin 100 mg, once daily for 52 weeks. Changes (mean ± SD) in HbA1c levels (NGSP levels) from baseline in the canagliflozin group in the double-blind study was -0.70 ± 0.82%. The incidence of adverse drug reactions of hypoglycaemia was 9.9% (7/71 patients).
The approved dosage and administration for CANAGLU® is 100 mg/day.

Efficacy in type 2 diabetes mellitus patient with renal impairment

1) Phase 3 study, Double-blind comparative study (Non-Japanese data)
Patients with type 2 diabetes mellitus not achieving adequate glycemic control through diet and exercise therapy with or without oral antihyperglycemic agents, who also had moderate renal impairment (eGFR ≥30 to <50 mL/min/1.73 m^2) (269 patients), received canagliflozin or placebo once daily for 26 weeks. The results are shown in the following table.
The incidences of hypoglycemic adverse drug reactions were 2.2% (2/90 patients) in the placebo group and 7.8% (7/90 patients) in the canagliflozin 100 mg group.

Table: Results of a placebo-controlled, double-blind, comparative study (at Week 26)

	Placebo n = 87		Canagliflozin 100 mg n = 88		
	Baseline	Change from baseline	Baseline	Change from baseline	Difference in change vs. Placebo
HbA1c (%)	8.02 ± 0.917	-0.03 ± 0.090	7.89 ± 0.898	-0.33 ± 0.090	-0.30 ± 0.117[#] [-0.529, -0.066]

Baseline values are presented as mean ± SD. Change from baseline and difference in change vs. placebo are presented as adjusted mean change ± SE and difference (Canagliflozin minus Placebo) between the changes ± SE, respectively. #P = 0.012, [ ]: two-sided 95% CI, HbA1c values are in NGSP units.

5.2 Pharmacokinetic properties

Plasma concentrations

1) Single administration
Plasma concentration over time and pharmacokinetic parameters after a single oral administration of canagliflozin 100 mg in type 2 diabetes mellitus patients 10 minutes before a meal are shown below.

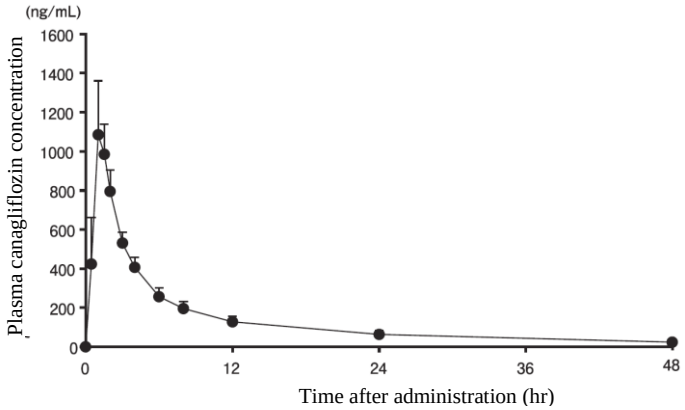

Figure: Time course of plasma concentration in patient with type 2 diabetes mellitus taking a single oral dose of 100 mg as canagliflozin (Mean + SD, n=12)

Table: Pharmacokinetic parameters in patients with type 2 diabetes mellitus taking a single oral dose of 100 mg as canagliflozin

C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
1126 (228)	6561 (1305)	1.0 (1.0–1.5)	10.2 (1.9)

n = 12; Mean (SD), t_{max}: Median (min–max)

2) Repeated administration

Pharmacokinetic parameters after repeated oral administration of canagliflozin 100 mg in type 2 diabetes mellitus patients once-daily for 14 days are shown below. Canagliflozin was estimated to reach steady state by day 4 after initiation of treatment.

Table: Pharmacokinetic parameters in patients with type 2 diabetes mellitus taking repeated oral doses once daily of 100 mg as canagliflozin for 14 days

C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
1136 (330)	6635 (1367)	1.0 (1.0–1.5)	11.8 (3.2)

n = 12; Mean (SD), t_{max}: Median (min–max)

3) Effects of food

When healthy adults received a single oral dose of canagliflozin 200 mg either in a fasted state or 10 minutes after eating (post-prandial administration), the geometric mean ratios for C_{max} and $AUC_{0-\infty}$ (post-prandial/fasting) and their 90% CI were 0.843 (0.790, 0.900) and 0.977 (0.945, 1.011). Compared to the fasted state, the median canagliflozin t_{max} value was approximately 1.0 hours longer for post-prandial administration.

Table: Pharmacokinetic parameters in healthy adults taking canagliflozin under fasting conditions or after a meal

	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	t_{max} (h)
Fasting	2026 (458)	15316 (3135)	2.0 (1.0–5.0)
Post-prandial	1740 (435)	15140 (3572)	3.0 (1.5–5.0)

n = 22 to 24; Mean (SD), t_{max}: Median (min–max)

Absorption (Non-Japanese Data)

Absolute bioavailability was about 65% after administration of a single oral dose of canagliflozin 300 mg to 9 healthy adults.

Distribution

The human plasma protein binding rate for canagliflozin was about 98% (*in vitro*, ultrafiltration method).

Metabolism

1) When 6 non-Japanese healthy adults received a single oral dose of 192 mg ^{14}C-labeled canagliflozin, total plasma radioactivity over 24 hours post-administration were composed of: unchanged drug (45.4–98.7%), glucuronic acid conjugate metabolites M5 (1.9–29.6%) and M7 (16.0–28.8%), and oxidative metabolite M9 (2.42–3.70%).
2) UGT1A9 and UGT2B4 were primarily involved in glucuronidation of canagliflozin in humans. Oxidative metabolism was primarily catalyzed by CYP3A4 followed by CYP2D6. Canagliflozin weakly inhibited CYP2B6, 2C8, 2C9, and 3A4 (IC_{50} value: 16, 75, 80 and 27 μmol/L), and did not inhibit CYP1A2, 2A6, 2C19, 2D6 and 2E1. There was no time-dependent inhibition of any CYP isoform, and no induction of CYP1A2, 2B6, 3A4, 2C9 and 2C19. Canagliflozin weakly inhibited UGT1A1 and 1A6 (IC_{50} value: 91 and 50 μmol/L), and did not inhibit UGT1A4, 1A9 and 2B7 (*in vitro*).

Excretion

1) When 6 non-Japanese healthy adults received a single oral dose of 192 mg ^{14}C-labeled canagliflozin, 32.5% of administered radioactivity was excreted in urine and 60.4% in feces over 168 hours post-administration. No unchanged canagliflozin was observed in urine up to 48 hours after administration, although M5 (13.3%) and M7 (17.2%) were observed. Canagliflozin (41.5%), M7 (3.2%), and M9 (7.0%) were observed in feces.
2) Canagliflozin was a substrate of P-glycoprotein, multidrug resistance-associated protein 2, and breast cancer resistance protein. Canagliflozin weakly inhibited P-glycoprotein and multidrug resistance-associated protein 2 (IC_{50} value: 19.3 μmol/L and 21.5 μmol/L) (*in vitro*).

Subjects with renal impairment

1) Subjects with type 2 diabetes mellitus and renal impairment
When type 2 diabetes mellitus subjects with moderate renal impairment received a single oral dose of 100 mg canagliflozin, $AUC_{0-\infty}$ was about 26% higher than for type 2 diabetes mellitus subjects with normal renal function. Also, mean change from baseline (mean [95% CI]) of total urinary glucose excretion up to 24 hours post-administration was 86.592 g [75.612, 97.572] for type 2 diabetes mellitus subjects with normal renal function, and 61.017 g [49.362, 72.671] with moderate renal impairment.

Table: Pharmacokinetic parameters after single oral dose in type 2 diabetes mellitus subjects with moderate renal impairment

Severity of renal impairment	n	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)
Subjects with normal renal function	12	1214 (338)	6929 (1734)
Type 2 diabetes mellitus subjects with moderate renal impairment (eGFR30 to 49 mL/min/1.73 m^2)	12	1197 (311)	8766 (2551)
Geometric mean ratio (%) to subjects with normal renal function [90% CI]		98 [82, 117]	126 [106, 149]

Mean (SD)

2) Subjects with renal impairment (Non-Japanese data)
When a single oral dose of 200 mg canagliflozin was administered to subjects with mild, moderate, or severe renal impairment, the canagliflozin C_{max} decreased compared to those with normal renal function by approximately 27%, 9%, and 10%, respectively. Furthermore, $AUC_{0-\infty}$ increased compared to those with normal renal function by approximately 15%, 29%, and 53%, respectively. In the end-stage renal failure, nearly no canagliflozin was eliminated by 4 hours of dialysis.

In addition, adjusted mean change from baseline of total urinary glucose excretion in 24 hours after administration in subjects with normal renal function and mild, moderate, or severe renal impairment was 53.04, 38.32, 17.11, and 4.27 g, respectively.

Table: Pharmacokinetic parameters after a single oral dose in subjects with renal impairment

Severity of renal impairment	n	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)
Normal renal function	3	1880 (475)	14862 (5380)
Mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2)	10	1469 (669)	17172 (6075)
Geometric mean ratio (%) with subjects with normal renal function [90% CI]		73 [50, 108]	115 [84, 159]
Moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2)	9	1717 (427)	18715 (4504)
Geometric mean ratio (%) with subjects with normal renal function [90% CI]		91 [61, 134]	129 [93, 178]
Severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2)	10	1746 (665)	22304 (5566)
Geometric mean ratio (%) with subjects with normal renal function [90% CI]		90 [61, 133]	153 [111, 211]
End-stage renal failure (post-dialysis)	8	1287 (277)	13587 (3216)
Geometric mean ratio (%) with subjects with normal renal function [90% CI]		69 [52, 90]	94 [67, 131]
End-stage renal failure (pre-dialysis)	8	1433 (509)	14205 (3648)
Geometric mean ratio (%) with subjects with normal renal function [90% CI]		75 [52, 107]	97 [67, 141]

Mean (SD)

Subjects with hepatic impairment (Non-Japanese data)

When subjects with impaired hepatic function received a single oral dose of 300 mg canagliflozin, canagliflozin C_{max} in those with mild hepatic impairment (Child-Pugh total score of 5–6) and moderate hepatic impairment (Child-Pugh total score of 7–9) was about 7% higher and about 4% lower, respectively, than in subjects with normal hepatic function. $AUC_{0-\infty}$ was about 10% and 11% higher, respectively, compared to subjects with normal hepatic function. There have been no clinical studies in subjects with severe hepatic impairment (Child-Pugh total score of >9).

Table: Pharmacokinetic parameters after a single oral dose in subjects with hepatic impairment

Severity of hepatic impairment	n	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)
Normal hepatic function	8[a]	2844 (794)	24632 (7132)
Mild hepatic impairment	8	3038 (670)	27162 (8609)
Geometric mean ratio (%) with subjects with normal hepatic function [90% CI]		107 [84, 137]	110 [86, 140]
Moderate hepatic impairment	8	2810 (1037)	26866 (5788)
Geometric mean ratio (%) with subjects with normal hepatic function [90% CI]		96 [75, 122]	111 [87, 141]

Mean (SD), a: $AUC_{0-\infty}$ n = 7

Pharmacokinetics in the elderly

A dose-finding study in Type 2 diabetes mellitus subjects compared dose-corrected canagliflozin plasma concentration trough values and $AUC_{0-2.17h}$ after 12-week administration in elderly (71-73 subjects 65 years of age and older) and non-elderly subjects (217-225 subjects under 65 years of age). The study found that mean trough concentrations were about 10-30% higher for elderly than non-elderly subjects.

Drug interactions

Effects of concomitant drugs on the pharmacokinetics of canagliflozin

1) Rifampicin (Non-Japanese data)

Table: Effects of rifampicin on the pharmacokinetics of canagliflozin

Concomitant drug	Concomitant drug dosage	Canagliflozin dosage	Concomitant drug pharmacokinetic parameters geometric mean ratio [90% CI] Concomitant use/monotherapy	
			C_{max}	$AUC_{0-\infty}$
Rifampicin	600 mg	300 mg	0.72 [0.61–0.84]	0.49 [0.44–0.54]

2) Other drugs (Non-Japanese data)
No substantial effects were noted in the combination studies of canagliflozin with teneligliptin*, metformin, cyclosporine, probenecid, oral contraceptives (ethinylestradiol and levonorgestrel), and hydrochlorothiazide.
*The data of teneligliptin were obtained with Japanese patients.

Effects of canagliflozin on the pharmacokinetics of concomitant drugs

1) Digoxin (Non-Japanese data)

Table: Effects of canagliflozin on pharmacokinetics of digoxin

Concomitant drug	Concomitant drug dosage	Canagliflozin dosage	Concomitant drug pharmacokinetic parameters geometric mean ratio [90% CI] Concomitant use/monotherapy	
			C_{max}	AUC_{0-24h}
Digoxin	0.25 mg	300 mg	1.36 [1.21–1.53]	1.20 [1.12–1.28]

2) Other drugs (Non-Japanese data)
No substantial effects were noted in the combination studies of canagliflozin with teneligliptin*, glibenclamide (glyburide), metformin, oral contraceptives (ethinylestradiol and levonorgestrel), hydrochlorothiazide, simvastatin, acetaminophen, or warfarin potassium).
*The data of teneligliptin were obtained with Japanese patients.
The approved dosage and administration for CANAGLU® is 100 mg/day.

5.3 Preclinical safety data

In a 2-year repeated-dose carcinogenicity study in male and female rats (10, 30, and 100 mg/kg/day), interstitial cell tumors of the testis were observed in male rats at dosages of 10 mg/kg/day and greater, while at doses of 100 mg/kg/day both male and female rats exhibited increased incidence of adrenal pheochromocytomas and renal tubular tumors. Exposure (AUC_{0-24h}) in rats administered this product 10 mg/kg/day (males) and 100 mg/kg/day (females) in repeated oral doses was approximately 6 and 84 times the maximum recommended clinical dose (100 mg once daily), respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-Mannitol, hydroxypropylcellulose, croscarmellose sodium, sodium stearyl fumarate, talc, polyvinyl alcohol (partially hydrolyzed), macrogol 4000, titanium oxide, yellow ferric oxide, red ferric oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

The products are packed into polyvinylchloride film / aluminum foil blister sheets of 10 tablets. 10 blister sheets are packaged in aluminum bags and then in carton box. A carton box contains 100 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKET AUTHORIZATION HOLDER

Mitsubishi Tanabe Pharma (Thailand) Co., Ltd.
Bangkok, Thailand

Manufactured by:

Mitsubishi Tanabe Pharma Factory Ltd.
Yoshitomi Plant, Fukuoka, Japan

Packaged and released by:

PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia.

8. MARKETING AUTHORIZATION NUMBERS

9. DATE OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT[1]

Warning according to the announcement of Ministry of Public Health

1. Do not use in people with known allergy to this medicine
2. Do not use for treatment of diabetes mellitus type 1, patients with ketoacidosis, patients with severe infection, patients having severe accident.
3. Pregnant women should avoid using this medicine and nursing women should be cautious of using this medicine
4. Should not use this medicine with alcoholic beverages.
5. If patients have nausea, vomiting, anorexia, stomachache, abnormal thirsty, weakness, difficult breath and confusion even though the level of blood sugar is not quite high, consult doctor or pharmacist as diabetic ketoacidosis may occur.
6. Should be cautions of bacterial and mycotic infection of genital and urinary tract system in patients using this medicine.

[1] Oct 2023