Luseogliflozin

Lusefi®

FORMULATION

Brand name	Lusefi 2.5 mg film-coated tablet	Lusefi 5 mg film-coated tablet
Ingredient	Luseogliflozin hydrate	
Content	Containing 2.5 mg as luseogliflozin per tablet	Containing 5 mg as luseogliflozin per tablet
Excipients	Lactose hydrate Microcrystalline cellulose Sodium starch glycolate Hydroxypropylcellulose Magnesium stearate Hypromellose Titanium oxide Macrogol 400 Carnauba wax Light anhydrous silicic acid	

PRODUCT DESCRIPTION

Brand name	Dosage form	Appearance, size, etc.		
Lusefi 2.5 mg film-coated tablet	White film-coated tablet	Front	Back	Side
				
		Diameter (mm)	Thickness (mm)	Weight (mg)
		Approximately 7.1	Approximately 3.2	Approximately 144
Lusefi 5 mg film-coated tablet	White film-coated tablet	Front	Back	Side
				
		Diameter (mm)	Thickness (mm)	Weight (mg)
		Approximately 8.6	Approximately 5.0	Approximately 286

Note) Use as prescribed by a doctor

INDICATIONS

Lusefi is indicated in the treatment of type 2 diabetes mellitus to improve glycemic control in adults as:

Monotherapy

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

Add-on combination therapy

In combination with glucose-lowering medicinal products including insulin preparations in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise plus monotherapy does not provide adequate glycemic control. (For study results with respect to combinations and effects on glycemic control see "CLINICAL STUDIES, 2. Add-on combination therapy")

DOSAGE AND ADMINISTRATION

Usually for adults, 2.5 mg as luseogliflozin should be orally administered once daily before or after breakfast. When the effect is insufficient, the dose can be increased to 5 mg once daily while closely monitoring the clinical course.

1. Patients with Renal Impairment

The efficacy of luseogliflozin 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. Lusefi is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2).

2. Patients with Hepatic Impairment

No dosage adjustment is necessary for patients with mild or moderate hepatic impairment.

3. Elderly

(1) Because physiological function is generally impaired in elderly patients, Lusefi should be administered carefully while monitoring the conditions of patients.
(2) Because detection of the symptoms of dehydration (including thirst) may be delayed in elderly patients, caution should be exercised.

4. Pediatric Population

The safety and efficacy of luseogliflozin in children aged 0 to < 20 years have not yet been established. No data are available.

CONTRAINDICATIONS (This drug is contraindicated in the following patients)

1. Patients with severe ketosis, diabetic coma or pre-coma [Administration of Lusefi is not appropriate because prompt correction of hyperglycemia by fluid or insulin is necessary]
2. Patients with severe infection, those who underwent or are scheduled for surgeries, those with serious trauma [Administration of Lusefi is not appropriate because plasma glucose control by insulin injection is desired]
3. Patients with a history of hypersensitivity to any of the ingredients of Lusefi

PRECAUTIONS

1. Special Precautions for Use (This drug should be administered with care in the following patients)

(1) The following patients or conditions [Hypoglycemia may occur]
  1) Pituitary dysfunction or adrenal insufficiency
  2) Poor nutritional status, starvation, irregular diet, insufficient dietary intake or debility
  3) Strenuous muscular exercise
  4) Patients who consume alcohol excessively
(2) Patients using other antidiabetic drugs (in particular, sulfonylureas or insulin preparations) [Hypoglycemia may occur in combined use (See "Important Precautions", "DRUG INTERACTIONS", "ADVERSE REACTIONS" and "CLINICAL STUDIES")]
(3) Patients with urinary tract infection or genital infection [Appropriate treatment should be provided before the administration of Lusefi because it may exacerbate the symptoms (See "Important Precautions")]
(4) Patients who are likely to develop dehydration (patients whose plasma glucose is controlled extremely poorly, elderly patients, patients concomitantly using diuretics, etc.) [Diuretic effect of Lusefi may lead to dehydration (See "Important Precautions", "DRUG INTERACTIONS", "ADVERSE REACTIONS" and "DOSAGE AND ADMINISTRATION")]

2. Important Precautions

(1) Before using Lusefi, hypoglycemic symptoms and the way to cope with them should be sufficiently explained to patients. In particular, when used with sulfonylureas or insulin preparations, risk of hypoglycemia may be increased. In combined use with sulfonylureas or insulin preparations, dose reduction of these drugs should be considered in order to decrease the risk of hypoglycemia associated with them. (See "Special Precautions for Use", "DRUG INTERACTIONS", "ADVERSE

Note) Use as prescribed by a doctor

REACTIONS" and "CLINICAL STUDIES")

(2) Use of Lusefi should be considered only for patients with established diagnosis of diabetes mellitus. It should be noted that there are diseases with diabetes-like symptoms such as impaired glucose tolerance and positive urinary glucose (renal glycosuria, thyroid dysfunction, etc.) other than diabetes mellitus.

(3) Use of Lusefi should be considered only when diet and exercise therapies, which are the basis of treatment of diabetes mellitus, were thoroughly used, but were not sufficiently effective.

(4) During the administration of Lusefi, plasma glucose and other parameters should be checked periodically to confirm its effect. When 3 months of the treatment is not sufficiently effective, a switch to a more appropriate treatment should be considered.

(5) The administration may become unnecessary or dose reduction may become necessary during the administration. The effect of administration may also be lost or become insufficient due to patients' lack of attention to their health or accompanying infections. Therefore, attention should be paid to dietary intake, plasma glucose, or presence or absence of infections and it should be constantly considered whether or not the administration can be continued as well as whether the dose and selection of drugs are appropriate.

(6) An increase in serum creatinine or a decrease in eGFR may be observed in the administration of Lusefi. Renal function should be checked periodically and in the treatment of patients with renal impairment, the course should be sufficiently monitored. (See "Special Precautions for Indications")

(7) Urinary tract infection and genital infection may occur and result in serious infections, such as pyelonephritis, necrotising fasciitis of the perineum (Fournier's gangrene) and sepsis. Genital infection, such as vaginal candidiasis, may occur. Onset of urinary tract infection and genital infection should be checked by sufficient observation and other methods. When they occur, appropriate treatment should be provided and interruption of administration or other measures should be considered depending on the conditions. The symptoms of urinary tract infection and genital infection and the way to cope with them should be explained to patients. (See "ADVERSE REACTIONS")

(8) Polyuria or pollakiuria may occur due to the diuretic action of Lusefi. Reduction of body fluid volume may occur. Patients should be instructed to drink fluid appropriately and be monitored sufficiently. When abnormalities including dehydration and decrease in blood pressure occur, appropriate measures including interruption of administration and fluid replacement should be taken. Especially in patients who are likely to have hypovolemia (including elderly patients and patients with combined use of diuretics), attention should be paid to the onset of events including dehydration, diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, and thromboembolism such as cerebral infarction. (See "Special Precautions for Use", "DRUG INTERACTIONS", "ADVERSE REACTIONS" and "DOSAGE AND ADMINISTRATION")

(9) Due to the mechanism of action of Lusefi, i.e., enhancement of urinary glucose excretion, fatty acid metabolism may be enhanced, which may lead to ketosis and ultimately ketoacidosis, even when plasma glucose is well controlled. Since marked increase in blood glucose levels may not be observed in this course, patients should be carefully monitored for the following conditions. (See "ADVERSE REACTIONS")

1) When nausea/vomiting, decreased appetite, abdominal pain, severe thirst, malaise, dyspnea or disturbance of consciousness is present, tests, including blood or urine ketone tests, should be performed. If any abnormality is noted, administration should be discontinued and appropriate treatment should be provided. It should be known to patients that ketoacidosis can develop even if blood sugar levels increased are not found.
2) In particular, when impaired insulin secretion, dose reduction or discontinuation of insulin therapy, excessive carbohydrate intake restriction, poor food intake, infection, or dehydration is present, patients should be closely monitored because ketoacidosis is likely to occur.
3) The symptoms of ketoacidosis (e.g., nausea/vomiting, decreased appetite, abdominal pain, severe thirst, malaise, dyspnea, disturbance of consciousness) should be explained to patients. Patients should be instructed to visit the medical institution immediately when any of these symptoms occur.

(10) Because weight decreased has been reported in association with the administration of Lusefi, attention should be paid to excessive weight loss.

(11) In patients with symptoms of dysuria, anuria, oliguria, or urinary retention, treatment of these symptoms should be prioritized and treatment with other drugs should be considered.

(12) There is no experience in the use for patients with severe liver dysfunction and safety in these patients has not been established.

(13) Efficacy and safety of combined use of Lusefi and GLP-1 receptor agonists have not been examined.

(14) Because hypoglycemic symptoms may occur, caution should be exercised in the administration to patients who work in high places or drive.

3. Precautions Concerning Use

When the drug is dispensed: In cases of drugs in PTP package, patients are instructed to remove the package and take the drug. (It has been reported that, when a sheet of PTP is mistakingly swallowed, sharp corners may pierce the esophageal mucosa, causing perforation and leading to a serious complications including mediastinitis)

4. Other Precautions

In the carcinogenicity study conducted by 104-week repeat oral administration of luseogliflozin at a dose of 4, 20, or 100 mg/kg/day in male and female rats, the incidence of pheochromocytoma in the adrenals, Leydig cell tumor in the testes and vascular tumors in the mesenteric lymph nodes was found to be increased in male animals treated at a dose of 100 mg/kg/day (equivalent to approximately 18 times the exposure [AUC] at the maximum recommended clinical dose (once daily administration of 5 mg)).

DRUG INTERACTIONS

Luseogliflozin is mainly metabolized by CYP3A4/5, 4A11, 4F2, 4F3B and UGT1A1. (See "PHARMACOKINETICS")

Note) Use as prescribed by a doctor

Precautions for co-administration (Caution should be exercised when considering the concomitant use of Lusefi with following drugs)

Names of drugs	Clinical symptoms and treatments	Mechanism and risk factors
Antidiabetic drugs Sulfonylureas, Biguanides, Thiazolidinediones, DPP-4 inhibitors, α-Glucosidase inhibitors, Glinides, GLP-1 receptor agonists, Insulin preparations, etc.	Because these drugs may cause hypoglycemia, they should be administered while closely monitoring plasma glucose and other conditions of patients. In combined use with sulfonylureas or insulin preparations, dose reduction of these drugs should be considered in order to reduce the risk of hypoglycemia associated with them. (See "Special Precautions for Use", "Important Precautions" and "ADVERSE REACTIONS") When hypoglycemic symptoms are observed, sucrose is usually administered. When α-glucosidase inhibitors are concomitantly used, glucose should be administered.	Hypoglycemic action is enhanced.
Drugs that enhance hypoglycemic action β-Blockers, Salicylic acids, MAO inhibitors, Fibrates, etc.	Because plasma glucose may be further decreased due to hypoglycemic action of the drugs shown in the left column, they should be administered with Lusefi while closely monitoring plasma glucose and other conditions of patients.	Hypoglycemic action is enhanced.
Drugs that weaken hypoglycemic action Adrenaline, Corticosteroid, Thyroid hormone, etc.	Because hypoglycemic action may be weakened due to hyperglycemic action of the drugs shown in the left column, they should be administered with Lusefi while closely monitoring plasma glucose and other conditions of patients.	Hypoglycemic action is weakened.
Diuretics Loop diuretics, Thiazide diuretics, etc.	Because diuretic action can be enhanced in combined use with Lusefi, caution should be exercised by, for example, adjusting the dose of diuretics as needed.	Diuretic action is enhanced.

ADVERSE REACTIONS

Adverse drug reactions including abnormal investigation findings were observed in 236 out of 1,262 subjects (18.7%) in clinical studies administered at 2.5 mg dose (including at increased dose of 5 mg) of luseogliflozin, at the time of approval in Japan. Major adverse drug reactions (adverse drug reactions observed in more than 2% of subjects) were pollakiuria in 35 subjects (2.8%), hypoglycemia in 30 subjects (2.4%), and β2-microglobulin urine increased in 26 subjects (2.1%).

1. Clinically Significant Adverse Reactions

(1) **Hypoglycemia** (1.0%*): Hypoglycemia may occur in combined use with other antidiabetic drugs (in particular, sulfonylureas or insulin preparations). In addition, hypoglycemia was reported without combined use of other antidiabetic drugs. When hypoglycemic symptoms are observed, appropriate measures such as eating food containing carbohydrates should be taken. However, when hypoglycemic symptoms are observed in combined use with α-glucosidase inhibitors, glucose should be administered. (See "Special Precautions for Use", "Important Precautions", "DRUG INTERACTIONS" and "CLINICAL STUDIES")

*: The incidence calculated from the results of clinical studies (monotherapy), at the time of approval in Japan

(2) **Pyelonephritis** (0.1%), **sepsis** (incidence unknown): Since pyelonephritis may occur and result in sepsis (including septic shock), patients should be closely monitored. If any abnormality is noted, administration should be discontinued and appropriate treatment should be provided. (See "Important Precautions")

(3) **Necrotising fasciitis of the perineum (Fournier's gangrene)** (incidence unknown): 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 necrotizing fasciitis. If Fournier's gangrene is suspected, Lusefi should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted. (See "Important Precautions")

(4) **Dehydration** (0.1%): Dehydration may occur. Patients should be instructed to drink fluid appropriately and be monitored sufficiently. When symptoms including thirst, polyuria, pollakiuria and blood pressure decreased appear and dehydration is suspected, appropriate measures including interruption of administration and fluid replacement should be taken. Since onset of thromboembolism such as cerebral infarction following dehydration has been reported, sufficient attention should be paid. (See "Special Precautions for Use" and "Important Precautions")

(5) **Ketoacidosis** (incidence unknown): Since ketoacidosis (including diabetic ketoacidosis) may occur, patients should be closely monitored. If any abnormality is noted, administration should be discontinued and appropriate treatment should be provided. (See "Important Precautions")

2. Other Adverse Reactions

The following adverse reactions have been reported in all the clinical trials and from post-marketing experience with luseogliflozin. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

	Common	Uncommon	Incidence unknown
Infections	Cystitis	Genital candidiasis, Urinary tract infection, Genital infection	
Blood system disorders		Polycythaemia	
Ear and labyrinth disorders			Vertigo
Vascular disorders		Hypotension	
Nervous system disorders		Dizziness postural, Dizziness, Headache	Sleepiness
Gastrointestinal disorders	Constipation	Diarrhoea, Gastrooesophageal reflux disease, Abdominal pain, Abdominal distension	Nausea, Vomiting, Abdominal discomfort
Skin and subcutaneous tissue disorders		Rash, Eczema	Pruritus, Urticaria
Musculoskeletal and connective tissue disorders		Muscle spasms	
Renal and urinary disorders	Pollakiuria	Polyuria	
Reproductive system and breast disorders		Pruritus genital	Balanoposthitis
General disorders		Thirst, Malaise	Feelings of weakness, Hunger
Investigations	Blood ketone body increased, β2-microglobulin urine increased, White blood cells urine positive, Albumin urine present	CRP increased, White blood cell count increased, Haematocrit increased, Haemoglobin increased, Urine ketone body present, Urine bacterial test positive, Blood urine present, Protein urine present, Red blood cells urine positive, Increase in NAG	Weight decreased, Blood creatinine increased

USE DURING PREGNANCY, DELIVERY OR LACTATION

(1) In pregnant women or women who may possibly be pregnant, Lusefi should not be administered and other drugs including insulin preparations should be used. [Safety for use during pregnancy has not been established. In animal studies (rats) of luseogliflozin, skeletal variations, delayed ossification, or membranous ventricular septum defect which were considered to be caused by a decrease in body weight of dams were observed in the oral administration at a dose of 150 mg/kg/day (equivalent to approximately 47 times the exposure [AUC] at the maximum recommended clinical dose (once daily administration of 5 mg)) or higher doses to pregnant animals. In animal studies (rats) of similar drugs, exposure of juvenile animals in the period corresponding to the mid to late pregnancy in humans was reported to cause dilatation of renal pelvis and renal tubule. In addition, transfer to fetuses was reported in animal studies (rats) of luseogliflozin]

(2) Nursing women should be recommended to avoid breastfeeding during the administration of this drug. [In animal studies (rats), secretion into breast milk was observed]

EFFECTS ON LABORATORY TESTS

Due to the mechanism of action of Lusefi, urinary glucose becomes positive and serum 1,5-AG (1,5-anhydroglucitol) is decreased during its administration. It should be noted that the test results of urinary glucose and serum 1,5-AG do not reflect plasma glucose control.

OVERDOSE AND TREATMENT

Single doses up to 25 mg (5 times the maximum recommended human dose) of luseogliflozin in healthy subjects was generally well-tolerated.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of luseogliflozin by haemodialysis has not been studied.

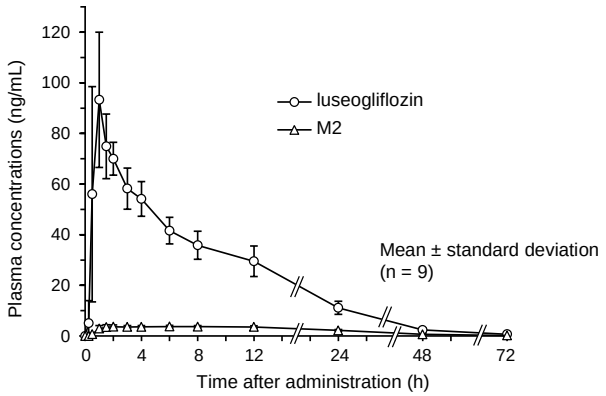
PHARMACOKINETICS

1. Plasma Concentrations

(1) Single administration[1)]

In single oral administration of luseogliflozin in fasting condition at a dose of 2.5 mg in healthy male adults, time-course change in plasma concentration and pharmacokinetic parameters of luseogliflozin and its active metabolite, M2, were as follows.

Note) Use as prescribed by a doctor



Dose	Analyte	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)
2.5 mg (n = 9)	Luseogliflozin	100 ± 22.3	1.11 ± 0.546	11.2 ± 1.05	1,000 ± 163
	M2	3.98 ± 0.538	5.44 ± 4.21	13.4 ± 1.11	122 ± 15.9

Mean ± standard deviation

(2) Repeat administration[2)]

In 7-day once-daily repeat oral administration of luseogliflozin at a dose of 2.5 mg or 5 mg in patients with type 2 diabetes mellitus, pharmacokinetic parameters of luseogliflozin were as follows. The molar ratio of the active metabolite, M2, to luseogliflozin calculated from the AUC_{0-24h} on Day 7 of the administration was 14.0% and 14.8% at doses of 2.5 mg and 5 mg, respectively.

Dose	Day of administration	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC* (ng·h/mL)
2.5 mg (n = 8)	Day 1	119 ± 27.0	0.625 ± 0.354	9.24 ± 0.928	864 ± 132
	Day 7	136 ± 42.0	1.00 ± 0.886	9.20 ± 0.710	899 ± 148
5 mg (n = 8)	Day 1	243 ± 45.7	0.625 ± 0.231	8.96 ± 1.11	1,690 ± 271
	Day 7	299 ± 50.3	0.688 ± 0.259	9.54 ± 1.26	1,880 ± 318

Mean ± standard deviation

*: $AUC_{0-\infty}$ on Day 1, AUC_{0-24h} on Day 7

(3) Effects of food intake[1)]

When luseogliflozin was orally administered in fasting condition, 5 minutes before breakfast (before meal) or 30 minutes after breakfast (after meal) in a single dose of 2.5 mg in healthy male adults (9 subjects), the geometric mean ratios of C_{max} and AUC_{0-72h} and their 90% confidence intervals were 0.790 [0.670, 0.933] and 0.986 [0.958, 1.01] for after meal/before meal, 0.922 [0.781, 1.09] and 0.980 [0.953, 1.01] for fasting/before meal, 0.857 [0.726, 1.01] and 1.01 [0.977, 1.04] for after meal/fasting, and 1.08 [0.919, 1.28] and 1.02 [0.991, 1.05] for before meal/fasting.

2. Protein Binding[3)]

The protein binding in human plasma was 96.0% to 96.3% at concentrations of 50 to 5,000 ng/mL (*in vitro*, ultracentrifugation).

3. Metabolism[4)-8)]

As the main metabolites in plasma and urine in oral administration of luseogliflozin in healthy male adults, *O*-deethyl form (M2), carboxyl form generated by oxidation after hydroxylation of the terminal carbon of ethyl group (M17), the glucuronide of luseogliflozin (M8), and the glucuronide of M2 (M12) were observed. M2 is the active metabolite which inhibits SGLT2. The 50% inhibitory concentration (IC_{50} value) of luseogliflozin and M2 for glucose uptake mediated by human SGLT2 (SGLT2-overexpressing cells) were 2.26 and 4.01 nmol/L, respectively (*in vitro*).

Metabolism of luseogliflozin was shown to mainly involve CYP3A4/5, 4A11, 4F2, 4F3B and UGT1A1 (*in vitro*).

Luseogliflozin showed weak inhibitory effect on CYP2C19 (IC_{50} value: 58.3 μmol/L), while it did not show any inhibitory effect on CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, or 3A4 (IC_{50} > 100 μmol/L) (*in vitro*). Luseogliflozin was shown not to induce CYP1A2 or 2B6, but to weakly induce CYP3A4 (*in vitro*). In a study in patients with type 2 diabetes mellitus using urinary 6β-hydroxycortisol concentration as a marker, luseogliflozin did not induce CYP3A4 (data in non-Japanese subjects).

4. Excretion[1),6)]

In single oral administration of luseogliflozin in fasting condition at a dose of 2.5 mg in healthy male adults (9 subjects), urinary excretion of luseogliflozin up to 72 hours after the administration was 4.47% (mean).

Luseogliflozin was shown to be a substrate of P-glycoprotein (P-gp), but not to be a substrate of breast cancer resistance protein (BCRP), organic anion transporting polypeptides (OATP1B1, OATP1B3), organic anion transporters (OAT1, OAT3) or organic cation transporter (OCT2). Luseogliflozin showed weak inhibitory effect on OATP1B3 (IC_{50} value: 93.1 μmol/L), while it did not show any inhibitory effect on P-gp, BCRP, OATP1B1, OAT1, OAT3, or OCT2 (IC_{50} > 100 μmol/L) (*in vitro*).

5. Patients with Renal Impairment [9),10)]

In single oral administration of luseogliflozin at a dose of 5 mg in type 2 diabetic subjects with renal impairment and type 2 diabetic patients with normal renal function, C_{max} showed a tendency toward decrease with decline of renal function.

Severity of renal impairment [eGFR*1]		C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	Urinary glucose excretion*2 (g)
Normal [≧90] (n = 11)		272 ± 86.4	0.545 ± 0.151	10.4 ± 0.832	2,010 ± 508	88.3 ± 36.9
Mild [60-89] (n = 17)		244 ± 53.4	1.01 ± 1.43	10.9 ± 0.752	2,070 ± 395	69.7 ± 19.1
Moderate	[45-59] (n = 10)	252 ± 67.5	0.650 ± 0.337	11.2 ± 2.68	2,160 ± 878	57.3 ± 14.9
	[30-44] (n = 13)	211 ± 62.5	1.58 ± 3.16	11.0 ± 1.49	2,060 ± 414	35.3 ± 10.8
Severe [15-29] (n = 6)		195 ± 63.1	2.00 ± 1.64	13.1 ± 3.62	2,420 ± 657	21.8 ± 7.10

Mean ± standard deviation

*1: Estimated glomerular filtration rate (mL/min/1.73 m^2)

*2: Change from baseline (the day before the administration) in cumulative urinary glucose excretion up to 24 hours after administration

6. Patients with Hepatic Impairment [11)]

In single oral administration of luseogliflozin at a dose of 5 mg in subjects with hepatic impairment that was up to moderate in severity and subjects with normal liver function, C_{max} was 23% lower in the subjects with moderate hepatic impairment than in the subjects with normal liver function.

Severity of hepatic impairment [Child-Pugh classification]	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)
Normal (n = 6)	228 ± 80.6	1.17 ± 1.40	11.0 ± 1.17	1,800 ± 427
Mild [Class A] (n = 8)	228 ± 54.9	0.500 ± 0.00	10.9 ± 1.14	1,720 ± 523
Moderate [Class B] (n = 5)	170 ± 28.4	0.500 ± 0.00	12.9 ± 1.85	1,780 ± 260

Mean ± standard deviation

7. Elderly Patients [12),13)]

In single oral administration of luseogliflozin at a dose of 5 mg in elderly subjects (24 men and women aged 65 years or older), C_{max} and $AUC_{0-\infty}$ (mean ± standard deviation) were 256 ± 63.6 ng/mL and 2,050 ± 307 ng·h/mL, respectively. In single oral administration of luseogliflozin at a dose of 5 mg in healthy male adults aged between 20 and 40 years (8 subjects) in another study, C_{max} and $AUC_{0-\infty}$ were 205 ± 53.5 ng/mL and 1,930 ± 290 ng·h/mL, respectively.

8. Drug Interactions [7),14),15)]

In combined use of luseogliflozin and various drugs in healthy male adults, the effects of combined use on pharmacokinetic parameters were as follows.

Co-administered drugs	Dose of co-administered drugs	Dose of luseogliflozin	Analyte	Geometric mean ratio (Ratio with/without co-administered drug)	
				C_{max} ratio [90% confidence interval]	$AUC_{0-\infty}$ ratio [90% confidence interval]
Glimepiride	1 mg single	5 mg single	Luseogliflozin (n = 12)	1.00 [0.898, 1.12]	1.00 [0.977, 1.03]
			Glimepiride (n = 12)	1.03 [0.949, 1.12]	1.07 [1.04, 1.10]
Metformin	250 mg single	5 mg single	Luseogliflozin (n = 12)	0.925 [0.845, 1.01]	0.985 [0.964, 1.01]
			Metformin (n = 12)	0.999 [0.897, 1.11]	1.04 [0.953, 1.14]
Voglibose	0.2 mg 3 times a day 7 days	5 mg single	Luseogliflozin (n = 12)	1.09 [0.984, 1.21]	0.999 [0.957, 1.04]
Miglitol	50 mg single	5 mg single	Luseogliflozin (n = 12)	0.851 [0.761, 0.952]	0.953 [0.931, 0.975]
			Miglitol (n = 12)	1.02 [0.915, 1.14]	1.04 [0.938, 1.16]
Pioglitazone	30 mg once daily 7 days	5 mg single	Luseogliflozin (n = 12)	1.16 [1.04, 1.30]	0.939 [0.897, 0.982]
			Pioglitazone (n = 12)	0.884 [0.746, 1.05]	0.896* [0.774, 1.04]
			Pioglitazone metabolite M-III (n = 12)	1.04 [0.973, 1.11]	1.01* [0.945, 1.07]
			Pioglitazone metabolite M-IV (n = 12)	1.01 [0.947, 1.07]	1.03* [0.977, 1.09]
Sitagliptin	50 mg single	5 mg single	Luseogliflozin (n = 12)	0.967 [0.914, 1.02]	0.986 [0.948, 1.03]
			Sitagliptin (n = 12)	0.983 [0.922, 1.05]	1.03 [1.01, 1.05]
Furosemide	40 mg once daily 4 days	5 mg single	Luseogliflozin (n = 12)	1.07 [0.980, 1.17]	1.13 [1.08, 1.18]
			Furosemide (n = 12)	1.36 [1.19, 1.54]	1.14* [1.07, 1.21]
Hydrochlorothiazide	25 mg once daily 4 days	5 mg single	Luseogliflozin (n = 12)	1.16 [1.04, 1.31]	1.11 [1.07, 1.16]
			Hydrochlorothiazide (n = 12)	1.09 [0.974, 1.23]	1.11* [1.08, 1.15]

*: AUC_{0-24h}

Note) Use as prescribed by a doctor

PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, fertility and early embryonic development, and pre- and postnatal development.

In the carcinogenicity study in mice, no neoplastic change related to luseogliflozin was observed at the highest dose of 100 mg/kg. The $AUC_{0\text{-}24h}$ values of luseogliflozin at this dose were 21 to 48 times higher than the AUC_T value in humans. On the other hand, in rats, the numbers of male animals with pheochromocytoma in the adrenals, those with Leydig cell tumor (benign) in the testes, and those with hemangioma/hemangiosarcoma in the mesenteric lymph nodes increased at the highest dose of 100 mg/kg. The $AUC_{0\text{-}24h}$ values of luseogliflozin at 20 mg/kg for males and 100 mg/kg for females, at which no neoplastic change was indicated, were 4.2 times higher in males and 40 times higher in females than AUC_T value in humans.

The increased number of rats with pheochromocytoma in the adrenals was probably explained by a change in calcium homeostasis due to persistent SGLT1 inhibition (increased calcium absorption) and increased food consumption (increased calcium consumption). Pheochromocytoma in the adrenals caused through this mechanism of action tends to occur in rats and is poorly extrapolated into humans. In addition, no effects of luseogliflozin on calcium have been reported in humans. It was, therefore, considered very unlikely that luseogliflozin would induce pheochromocytoma in the adrenals in humans.

Leydig cell tumor in the testes was likely caused by increased luteinizing hormone levels due to decreased testosterone levels resulting from long-term repeated administration of luseogliflozin. However, this tumor caused through the above mechanism of action is specific to rats and is poorly extrapolated into humans. It was, therefore, considered very unlikely that luseogliflozin would lead to the occurrence of Leydig cell tumor in humans.

Hemangioma/hemangiosarcoma in the mesenteric lymph nodes was likely caused by the following. The testing facility of the rat carcinogenicity study was prone to develop these tumors in the mesenteric lymph nodes. In addition, it was also suspected that these tumors occurred due to secondary factors, including local ischemia, caused by malnutrition and stress, such as decreased body weight and increased urinary glucose excretion. It was, however, considered very unlikely that luseogliflozin would induce hemangioma/hemangiosarcoma in humans.

In the embryo-fetal development study in rats, low body weight, skeletal variations, delayed ossification, and membranous ventricular septum defect at 150 mg/kg or 500 mg/kg were changes secondary to malnutrition or exacerbation of general condition of dams due to treatment with luseogliflozin. The $AUC_{0\text{-}24h}$ value of luseogliflozin at 50 mg/kg, at which no teratogenicity was indicated, was 15 times higher than the AUC_T value in humans.

CLINICAL STUDIES

1. Monotherapy

(1) Double-blind placebo-controlled study (dose-finding study)[16),17)]

To patients with type 2 diabetes mellitus whose plasma glucose is insufficiently controlled by diet and exercise therapies (280 subjects), 1 mg, 2.5 mg, 5 mg, or 10 mg of luseogliflozin or placebo was orally administered once daily before breakfast for 12 weeks. When changes compared with the value before the administration were examined, luseogliflozin significantly lowered HbA1c (NGSP value) compared with placebo.

	HbA1c (NGSP value) (%)			Fasting plasma glucose (mg/dL)		2-hour postprandial plasma glucose (mg/dL)	
	At the start of administration	Change from the value before the administration	Difference from placebo	Change from the value before the administration	Difference from placebo	Change from the value before the administration	Difference from placebo
Placebo (n = 57)	7.92 ± 0.84	0.22 [0.10, 0.34]	-	8.1 [2.6, 13.6]	-	3.7 [- 6.8, 14.3]	-
Luseogliflozin 2.5 mg (n = 56)	8.05 ± 0.75	- 0.39 [- 0.51, - 0.27]	- 0.61# [- 0.78, - 0.44]	- 16.8 [- 22.3, - 11.3]	- 24.9# [- 32.7, - 17.1]	- 52.7 [- 63.5, - 41.9]	- 56.4# [- 71.6, - 41.3]
Luseogliflozin 5 mg (n = 54)	7.86 ± 0.69	- 0.46 [- 0.58, - 0.34]	- 0.68# [- 0.85, - 0.51]	- 21.0 [- 26.7, - 15.3]	- 29.1# [- 37.0, - 21.2]	- 55.4 [- 66.5, - 44.3]	- 59.2# [- 74.5, - 43.8]

At the start of administration: mean ± standard deviation
Change from the value before the administration, difference from placebo: least squares mean
#: $p < 0.001$ (unrestricted LSD method using the value at the start of treatment as a covariate), 2-sided 95% confidence interval shown in [ ]

(2) Double-blind placebo-controlled study (confirmatory study)[18)]

To patients with type 2 diabetes mellitus whose plasma glucose is insufficiently controlled by diet and exercise therapies (158 subjects), 2.5 mg of luseogliflozin or placebo was orally administered once daily before breakfast for 24 weeks. When changes compared with the value before the administration were examined, luseogliflozin significantly lowered HbA1c (NGSP value) compared with placebo.

	HbA1c (NGSP value) (%)			Fasting plasma glucose (mg/dL)		2-hour postprandial plasma glucose (mg/dL)	
	At the start of administration	Change from the value before the administration	Difference from placebo	Change from the value before the administration	Difference from placebo	Change from the value before the administration	Difference from placebo
Placebo (n = 79)	8.17 ± 0.80	0.13 [- 0.04, 0.29]	-	- 0.8 [- 5.4, 3.7]	-	1.1 [- 8.0, 10.1]	-
Luseogliflozin 2.5 mg (n = 79)	8.14 ± 0.91	- 0.63 [- 0.79, - 0.46]	- 0.75# [- 0.99, - 0.52]	- 28.3 [- 32.9, - 23.8]	- 27.5# [- 33.9, - 21.1]	- 55.8 [- 64.7, - 46.8]	- 56.8# [- 69.6, - 44.1]

At the start of administration: mean ± standard deviation
Change from the value before the administration, difference from placebo: least squares mean
#: p < 0.001 (analysis of covariance using the value at the start of treatment as a covariate), 2-sided 95% confidence interval shown in [ ]

(3) Long-term studies[19),20)]
To patients with type 2 diabetes mellitus whose plasma glucose is insufficiently controlled by diet and exercise therapies (299 subjects), 2.5 mg or 5 mg (when the dose was increased) of luseogliflozin was orally administered once daily before breakfast for 52 weeks (HbA1c (NGSP value) at the start of administration: 7.67% ± 0.66%). Luseogliflozin lowered HbA1c (NGSP value) starting from early in the administration and the change in HbA1c (NGSP value) at Week 52 from the start of the administration (mean (2-sided 95% confidence interval)) was - 0.50 (- 0.6, - 0.4)%. Stable glycemic control was achieved throughout the 52 weeks. The incidence of the adverse drug reaction of hypoglycemia was 1.3% (4/299 subjects).

2. Add-on combination therapy

(1) Long-term study of luseogliflozin in add-on combination with sulfonylurea[21),22)]
To patients with type 2 diabetes mellitus whose plasma control was insufficiently controlled by diet and exercise therapies and monotherapy with glimepiride (150 subjects), 2.5 mg or 5 mg (when the dose was increased) of luseogliflozin was orally administered once daily before breakfast for 52 weeks. Luseogliflozin lowered HbA1c (NGSP value) starting from early in the administration. Stable glycemic control was achieved throughout the 52 weeks in combined use with glimepiride.

	HbA1c (NGSP value) (%)			
	At the start of administration	At 24 weeks		At 52 weeks
		Change from the value before the administration	Difference from placebo	Change from the value before the administration
Placebo (n = 71)	8.01 ± 0.73	0.40 [0.2, 0.6]	-	-
Luseogliflozin 2.5 mg (n = 150)	8.07 ± 0.85	- 0.50 [- 0.6, - 0.4]	- 0.88 # [- 1.0, - 0.7]	- 0.63 [- 0.8, - 0.5]

At the start of administration: mean ± standard deviation
Change from the value before the administration: mean, difference from placebo: least squares mean
#: p < 0.001 (analysis of covariance using the value at the start of treatment as a covariate), 2-sided 95% confidence interval shown in [ ]

The incidence of the adverse drug reaction of hypoglycemia was 8.7% (13/150 subjects) in combined use with glimepiride.

(2) Long-term study of luseogliflozin in add-on combination with oral hypoglycemic drugs[23)]
To patients with type 2 diabetes mellitus whose plasma control was insufficiently controlled by diet and exercise therapies and monotherapy with oral hypoglycemic drugs (biguanide (117 subjects), thiazolidinedione (95 subjects), DPP-4 inhibitor (111 subjects), α-glucosidase inhibitor (105 subjects), glinide (59 subjects)), 2.5 mg or 5 mg (when the dose was increased) of luseogliflozin was orally administered once daily before breakfast for 52 weeks. Luseogliflozin lowered HbA1c (NGSP value) starting from early in the administration. Stable glycemic control was achieved throughout the 52 weeks in combined use with any of the oral hypoglycemic drugs examined.

Concomitant drugs	HbA1c (NGSP value) (%)	
	At the start of administration	Change from the value before the administration at Week 52
Biguanide (n = 117)	7.84 ± 0.71	- 0.61 [- 0.7, - 0.5]
Thiazolidinedione (n = 95)	7.95 ± 0.92	- 0.60 [- 0.8, - 0.4]
DPP-4 inhibitor (n = 111)	7.88 ± 0.78	- 0.52 [- 0.6, - 0.4]
α-Glucosidase inhibitor (n = 105)	7.85 ± 0.77	- 0.68 [- 0.8, - 0.5]
Glinide (n = 59)	8.00 ± 0.88	- 0.59 [- 0.8, - 0.4]

At the start of administration: mean ± standard deviation
Change from the value before the administration: mean, 2-sided 95% confidence interval shown in [ ]

The incidence of the adverse drug reaction of hypoglycemia was 2.6% (3/117 subjects) in combined use with biguanide, 2.1% (2/95 subjects) in combined use with thiazolidinedione, 0.9% (1/111 subjects) in combined use with DPP-4 inhibitor and 1.7% (1/59 subjects) in combined use with glinide. No hypoglycemia was observed in combined use with α-glucosidase inhibitor.

(3) Long-term study of luseogliflozin in add-on combination with insulin preparations[24),25)]
To patients with type 2 diabetes mellitus whose plasma control was insufficiently controlled by diet and exercise therapies and insulin preparations (233 subjects), 2.5 mg of luseogliflozin or placebo was orally administered once daily before breakfast for 16 weeks. The results were as the following table. The incidence of the adverse drug reaction of hypoglycemia were 10.8% in the placebo group (8/74 subjects) and 18.9% in the luseogliflozin group (30/159 subjects).

	HbA1c (NGSP value) (%)				
	At the start of administration	16 weeks [a]		End of treatment [b]	
		Change from the value before the administration	Difference from placebo	Change from the value before the administration	Difference from placebo
Placebo (n = 74)	8.84 ± 0.83	0.29 [0.1, 0.5]	-	0.39 [0.22, 0.56]	-
Luseogliflozin 2.5 mg (n = 159)	8.70 ± 0.83	- 0.77 [- 0.9, - 0.6]	- 1.07 # [- 1.3, - 0.9]	- 0.74 [- 0.87, - 0.62]	- 1.18 # [- 1.39, - 0.98]

At the start of administration: mean ± standard deviation
Change from the value before the administration, difference from placebo: least squares mean
a: at 16 weeks from the start of the administration
b: at the end of treatment period
#: $p < 0.001$ (analysis of covariance using the value at the start of treatment as a covariate), 2-sided 95% confidence interval shown in [ ]

In patients who were administered with luseogliflozin continuously for 52 weeks as the result of assignment in the luseogliflozin group in the double-blind treatment period for 16 weeks and proceeding to the open-label treatment period for 36 weeks, change in HbA1c (NGSP value) (mean [2-sided 95% confidence interval]) was - 1.00% (- 1.1%, - 0.9%) from the start of the administration. The incidence of the adverse drug reaction of hypoglycemia was 29.6% (47/159 subjects) in the 52 weeks administration group.

3. Efficacy in Patients with Renal Impairment[26)]
When 2.5 mg of luseogliflozin or placebo was orally administered once daily before breakfast for 24 weeks in type 2 diabetic patients with moderate renal impairment (eGFR, 30 mL/min/1.73 m^2 or higher, 59 mL/min/1.73 m^2 or lower) (145 subjects), change in HbA1c was as follows.

	HbA1c (NGSP value) (%)		
	At the start of administration	Change from the value before the administration	Difference from placebo
Placebo (n = 50)	7.69 ± 0.65	0.09 [- 0.1, 0.3]	-
Luseogliflozin 2.5 mg (n = 95)	7.72 ± 0.68	- 0.11 [- 0.2, 0.0]	- 0.19♭ [- 0.4, 0.0]

At the start of administration: mean ± standard deviation
Change from the value before the administration, difference from placebo: least squares mean
♭ : $p < 0.05$ (analysis of covariance using the value at the start of treatment as a covariate), 2-sided 95% confidence interval shown in [ ]

When, in addition to the above administration, 2.5 mg or 5 mg (when the dose was increased) of luseogliflozin was administered once daily for 28 weeks (52 weeks in total) (95 subjects) (HbA1c (NGSP value) at the start of the administration: 7.72% ± 0.68%), change from the start of the administration in HbA1c (NGSP value) (mean (2-sided 95% confidence interval)) was - 0.30 (- 0.4, - 0.2)%.

PHARMACOLOGY

1. Mechanism of Action[27),28)]
Luseogliflozin lowers plasma glucose by inhibiting the activity of sodium-glucose cotransporter 2 (SGLT2) which is involved in reabsorption of glucose at renal proximal tubules and promoting the excretion of excessive glucose in blood into urine.

2. SGLT2 Inhibition[29),30)]
Luseogliflozin selectively inhibited the glucose uptake mediated by human SGLT2 (SGLT2-overexpressing cells) (Ki value: 1.1 nmol/L) (*in vitro*).

3. Urinary Glucose Excretion[2),28),31),32)]
(1) In obese type 2 diabetes models (Zucker Fatty rats and db/db mice), single oral administration increased urinary glucose excretion (8 or 24 hours after the administration). In a non-obese type 2 diabetes model (GK rats), dietary administration for 20 weeks increased urinary glucose excretion (24 hours after the administration).

(2) To patients with type 2 diabetes mellitus, 2.5 mg or 5 mg of luseogliflozin or placebo was orally administered once daily before breakfast for 7 days. Luseogliflozin increased urinary glucose excretion up to 24 hours after the administration compared with placebo.

4. Hypoglycemic Action[2),28),32),33)]
(1) In an obese type 2 diabetes model (Zucker Fatty rats), single oral administration inhibited the increase in plasma glucose after glucose loading. In another obese type 2 diabetes model (db/db mice), once-daily repeat oral administration for 4

weeks decreased the change in glycated hemoglobin from baseline. In a non-obese type 2 diabetes model (GK rats), dietary administration for 20 weeks decreased glycated hemoglobin.

(2) To patients with type 2 diabetes mellitus, 2.5 mg or 5 mg of luseogliflozin or placebo was orally administered once daily before breakfast for 7 days. Luseogliflozin improved plasma glucose AUC 4 hours after breakfast, lunch, or dinner and fasting plasma glucose compared with placebo.

PHYSICOCHEMISTRY

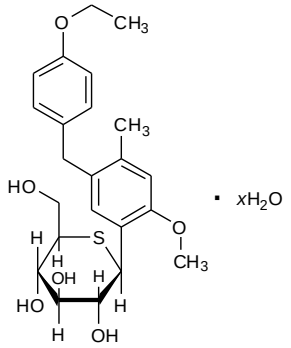
Generic name:

Luseogliflozin Hydrate (JAN)
luseogliflozin (INN)

Chemical name:

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-{5-[(4-Ethoxyphenyl)methyl]-2-methoxy-4-methylphenyl}-6-(hydroxymethyl)thiane-3,4,5-triol hydrate

Structural formula:



Molecular formula: $C_{23}H_{30}O_6S \cdot xH_2O$

Molecular weight: 434.55 (as anhydrate)

Description: White powder. It is very soluble in *N*,*N*-dimethylformamide, sparingly soluble in acetonitrile, methanol, or ethanol (99.5), and practically insoluble in water. It gradually turns pale yellowish white in light.

Melting point: 159.0°C

PACKAGING

Lusefi 2.5 mg film-coated tablets: PTP 100 tablets

Lusefi 5 mg film-coated tablets: PTP 100 tablets

STORAGE CONDITION

Store below 30℃.

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Note) Use as prescribed by a doctor

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33) Company data (lowering effect on glycated hemoglobin in db/db mice)

Manufactured by
Taisho Pharmaceutical Co., Ltd. Omiya Factory
403, Yoshino-cho 1-chome, Kita-ku, Saitama-shi, Saitama, Japan

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