SUMMARY OF PRODUCT CHARACTERISTICS

Luseogliflozin

Luseco® 2.5mg film-coated tablet
Luseco® 5mg film-coated tablet

Blood Glucose Lowering Drug

Rx

1. NAME OF THE MEDICINAL PRODUCT

Luseogliflozin (Luseco) 2.5 mg film-coated tablet
Luseogliflozin (Luseco) 5 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.5 mg:
Each tablet of Luseogliflozin (Luseco) contains 2.5 mg of luseogliflozin (as luseogliflozin hydrate).

Excipient with known effect:

Each tablet contains lactose monohydrate equivalent to 69.4 mg of lactose anhydrous.

For a full list of excipients, see section 6.1.

5 mg:
Each tablet of Luseogliflozin (Luseco) contains 5 mg of luseogliflozin (as luseogliflozin hydrate).

Excipient with known effect:

Each tablet contains lactose monohydrate equivalent to 138.7 mg of lactose anhydrous.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

2.5 mg:
Round, biconvex, diameter 7.1 mm, white, film-coated tablet imprinted with “LGF 2.5” on one side.

5 mg:
Round, biconvex, diameter 8.6 mm, white, film-coated tablet imprinted with “LGF 5” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Luseogliflozin (Luseco) is indicated as adjunct treatment to diet and exercise in the glycemic control of adults with type 2 diabetes mellitus.

4.2 Posology and method of administration

Posology
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.

Luseogliflozin (Luseco) should be administered with care in patients using other antidiabetic drugs (in particular, sulfonylureas, insulin preparations or GLP-1 receptor agonists) [hypoglycemia may occur with combined use.]

In particular, when used with sulfonylureas, insulin preparations or GLP-1 receptor agonists, risk of hypoglycemia may be increased. In combined use with sulfonylureas, insulin preparations or GLP-1 receptor agonists, dose reduction of these drugs should be considered in order to decrease the risk of hypoglycemia associated with them (see sections 4.5, 4.8 and 5.1).

Patients with renal impairment
Luseogliflozin (Luseco) should not be administered to patients with severe renal impairment or patients with end-stage renal failure being treated by dialysis because it is not expected to be effective in these patients.

The necessity of administration should be carefully considered in patients with moderate renal impairment because Luseogliflozin (Luseco) may not be sufficiently effective (see sections 4.4, 5.1 and 5.2).

Patients with hepatic impairment
There is no experience in the use for patients with severe liver dysfunction and safety in these patients has not been established (see sections 4.4 and 5.2).

Paediatric population
Safety in the use in low-birth-weight babies, neonates, nursing infants, infants, and children has not been established. [There is no experience in the use for the above patients.]

Elderly
Because physiological function is generally impaired in elderly patients, Luseogliflozin (Luseco) should be administered carefully while monitoring the conditions of patients.

Because detection of the symptoms of dehydration (including thirst) may be delayed in elderly patients, caution should be exercised (see section 4.4).

Method of administration
Luseogliflozin (Luseco) should be orally administered once daily, before or after breakfast.

4.3 Contraindications

Patients with a history of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General
Luseogliflozin (Luseco) should be used only in patients diagnosed with type 2 diabetes mellitus and should not be administered to patients with type 1 diabetes mellitus.

Use of Luseogliflozin (Luseco) 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.

Use in patients with renal impairment
An increase in serum creatinine or a decrease in eGFR may be observed in the administration of Luseogliflozin (Luseco). Renal function should be checked periodically and in the treatment of patients with renal impairment, the course should be sufficiently monitored (see sections 4.2, 5.1 and 5.2).

Use in patients with hepatic impairment
There is no experience in the use for patients with severe liver dysfunction and safety in these patients has not been established (see sections 4.2 and 5.2).

Use in patients at risk for volume depletion
Luseogliflozin (Luseco) should be administered with care in 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 Luseogliflozin (Luseco) may lead to dehydration.]

Polyuria or pollakiuria may occur due to the diuretic action of Luseogliflozin (Luseco). Reduction of body fluid volume may occur. Patients should be 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 sections 4.2, 4.5 and 4.8).

Urinary tract infections and genital infections
Luseogliflozin (Luseco) should be administered with care in patients with urinary tract infection or genital infection [It may exacerbate the symptoms.]

Urinary tract infection and genital infection may occur and result in serious infections, such as pyelonephritis, necrotizing 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 with sufficient observations 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 (see section 4.8).

Ketoacidosis
Due to the mechanism of action of Luseogliflozin (Luseco), 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 section 4.8).

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.

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.

Urine laboratory assessments
Due to the mechanism of action of Luseogliflozin (Luseco), urinary glucose becomes positive during its administration.

Macrovascular outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Luseogliflozin (Luseco).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Antidiabetic drugs (Sulfonylureas, Biguanides, Thiazolidinediones, DPP-4 inhibitors, α -Glucosidase inhibitors, Glinide, 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, insulin preparations or GLP-1 receptor agonists, dose reduction of these drugs should be considered in order to reduce the risk of hypoglycemia associated with them.
When hypoglycemic symptoms are observed, sucrose is usually administered. When α-glucosidase inhibitors are concomitantly used, glucose should be administered (see sections 4.4 and 4.8).

Diuretics (Loop diuretics, Thiazide diuretics, etc.)
Because diuretic action can be enhanced in combined use with luseogliflozin, caution should be exercised by, for example, adjusting the dose of diuretics as needed (see section 4.4).

Pharmacokinetic interactions
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).

Effect of other medicinal products on luseogliflozin
Interaction in combined use of luseogliflozin and 6 representative existing oral hypoglycemic drugs (glimepiride, metformin, voglibose, miglitol, pioglitazone, and sitagliptin) was investigated in healthy Japanese male adults. Pharmacokinetics of luseogliflozin was considered not to be influenced greatly by other drugs used concomitantly.

Effects of luseogliflozin on other medicinal products
Interaction in combined use of luseogliflozin and 6 representative existing oral hypoglycemic drugs (glimepiride, metformin, voglibose, miglitol, pioglitazone, and sitagliptin) was investigated in healthy Japanese male adults. Luseogliflozin was considered not to greatly influence the pharmacokinetics of other drugs used in combination with luseogliflozin.

Drug/Laboratory test interference
1,5-AG assay
Due to the mechanism of action of luseogliflozin, 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.

4.6 Pregnancy and lactation

- In pregnant women or women who may possibly be pregnant, Luseogliflozin (Luseco) should not be administered and other drugs including insulin preparations should be used. [Safety for use during pregnancy has not been established. And transfer to

fetuses was reported in animal studies (rats) of luseogliflozin.]

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

In all the clinical trials of patients with Type 2 diabetes mellitus in Japan (TS071-02-1, TS071-02-3, TS071-03-1, TS071-03-2, TS071-03-3, TS071-03-4, TS071-03-5), adverse reactions including abnormal investigation findings were observed in 236 out of 1262 subjects (18.7%) administered at 2.5 mg dose (including at increased dose of 5 mg) of luseogliflozin. Major adverse reactions (adverse reactions observed in more than 2% of subjects) were pollakiuria (35 cases, 2.8%), hypoglycemia (30 cases, 2.4%), and β2 microglobulin urine increased (26 cases, 2.1%). Adverse reactions related to cardiovascular disorders were observed in 12 patients (1.0%). [At the time of approval in Japan]

Tabulated list of adverse reactions

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

Table 1. Adverse reactions in all the clinical trials and from post-marketing experience with Luseogliflozin (Luseco)

	Common	Uncommon	Incidence unknown
Infections	Cystitis	Genital candidiasis, Urinary tract infection, Pyelonephritis, Genital infection	Sepsis
Blood system disorders		Polycythaemia	
Metabolism and nutrition disorders	Hypoglycaemia	Dehydration	Ketoacidosis
Nervous system disorders		Dizziness postural, Dizziness, Headache	
Ear and labyrinth disorders			Vertigo
Vascular disorders		Hypotension	
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	Balanopostitis
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

Clinically significant adverse reactions

Hypoglycemia

Hypoglycemia may occur in combined use with other antidiabetic drugs (in particular, sulfonylureas, insulin preparations or GLP-1 receptor agonists). 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 sections 4.4, 4.5 and 5.1).

Pyelonephritis, sepsis, necrotizing fasciitis of the perineum (Fournier's gangrene)
Pyelonephritis may occur and may result to sepsis (including septic shock). Onset of Fournier's gangrene, rare but serious infection requiring urgent surgical intervention, has been reported in patients with diabetes mellitus receiving other sodium-glucose cotransporter 2 (SGLT2) inhibitors. Patients should be closely monitored. If any abnormality is noted, administration should be discontinued and appropriate treatment should be provided (see section 4.4).

Dehydration
Dehydration may occur. Patients should 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 section 4.4).

Ketoacidosis
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 section 4.4).

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
Luseogliflozin lowers plasma glucose by inhibiting the activity of SGLT2 which is involved in reabsorption of glucose at renal proximal tubules and promoting the excretion of excessive glucose from the blood into the urine. Luseogliflozin selectively inhibited the glucose uptake mediated by human SGLT2 (SGLT2-overexpressing cells) (Ki value: 1.1 nmol/L) (*in vitro*).

Pharmacodynamic effects
Urinary Glucose Excretion
- 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).
- 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.

Hypoglycemic Action
- 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.
- 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.

Clinical efficacy and safety
Monotherapy
(1) Double-blind placebo-controlled study (dose-finding study)

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 (Luseco) significantly lowered HbA1c (NGSP value) compared with placebo.

Table 2. Results of double-blind placebo-controlled study (dose-finding study)

	Monotherapy		
	Placebo	Luseogliflozin (Luseco) 2.5 mg	Luseogliflozin (Luseco) 5 mg
N	57	56	54
HbA1c (NGSP value) (%)			
Baseline [a]	7.92± 0.84	8.05 ± 0.75	7.86 ± 0.69
Change from baseline [b]	0.22 [0.10, 0.34]	- 0.39 [- 0.51, - 0.27]	- 0.46 [- 0.58, - 0.34]
Difference from placebo [b]	-	- 0.61[#]	- 0.68[#]

		[- 0.78, - 0.44]	[- 0.85, - 0.51]
Fasting plasma glucose (mg/dL)			
Change from baseline [b]	8.1 [2.6, 13.6]	- 16.8 [- 22.3, - 11.3]	- 21.0 [- 26.7, - 15.3]
Difference from placebo [b]	-	- 24.9[#] [- 32.7, - 17.1]	- 29.1[#] [- 37.0, - 21.2]
2-hour postprandial plasma glucose (mg/dL)			
Change from baseline [b]	3.7 [- 6.8, 14.3]	- 52.7 [- 63.5, - 41.9]	- 55.4 [- 66.5, - 44.3]
Difference from placebo [b]	-	- 56.4[#] [- 71.6, - 41.3]	- 59.2[#] [- 74.5, - 43.8]

a: mean ± standard deviation

b: least squares mean

#: p < 0.001(unrestricted LSD method using the baseline value as a covariate), 2-sided 95% confidence interval shown in [ ]

(2) Double-blind placebo-controlled study (confirmatory study)

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 (Luseco) significantly lowered HbA1c (NGSP value) compared with placebo.

Table 3. Results of double-blind placebo-controlled study (confirmatory study)

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

a: mean ± standard deviation

b: least squares mean

#: p < 0.001 (unrestricted LSD method using the baseline value as a covariate), 2-sided 95% confidence interval shown in [ ]

(3) Long-term studies

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 (Luseco) 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).

Concomitant Therapy

(1) Long-term study of Luseogliflozin (Luseco) in add-on combination with oral hypoglycemic drugs

To patients with type 2 diabetes mellitus whose plasma control was insufficiently controlled by diet and exercise therapies and monotherapy with oral hypoglycemic drugs (sulfonylurea [150 subjects], biguanide [117 subjects], thiazolidinedione [95 subjects], α-glucosidase inhibitor [105 subjects], DPP-4 inhibitor [111 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 (Luseco) 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.

Table 4. Results at Week 52 of studies of Luseogliflozin (Luseco) in add-on combination with oral hypoglycemic drugs

Concomitant drugs	N	HbA1c (NGSP value) (%)	
		Baseline [a]	Change from baseline at Week 52 [b]
Sulfonylurea	150	8.07 ± 0.85	- 0.63 [- 0.8, - 0.5]
Biguanide	117	7.84 ± 0.71	- 0.61 [- 0.7, - 0.5]
α-Glucosidase inhibitor	105	7.85 ± 0.77	- 0.68 [- 0.8, - 0.5]

Thiazolidinedione	95	7.95 ± 0.92	- 0.60 [- 0.8, - 0.4]
DPP-4 inhibitor	111	7.88 ± 0.78	- 0.52 [- 0.6, - 0.4]
Glinide	59	8.00 ± 0.88	- 0.59 [- 0.8, - 0.4]

a: mean ± standard deviation

b: mean, 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 sulfonylurea, 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.

(2) Long-term study of Luseogliflozin (Luseco) in add-on combination with insulin preparations

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 hypoglycemia as an adverse drug reaction were 10.8% in the placebo group (8/74 subjects) and 18.9% in the Luseogliflozin (Luseco) group (30/159 subjects).

Table 5. Results of long-term study of Luseogliflozin (Luseco) in add-on combination with insulin preparations

	Placebo	Luseogliflozin (Luseco) 2.5 mg
N	74	159
HbA1c (NGSP value) (%)		
Baseline [a]	8.84 ± 0.83	8.70 ± 0.83
Change from baseline [b, c]	0.29 [0.1, 0.5]	- 0.77 [- 0.9, - 0.6]
Difference from placebo [b, c]	-	- 1.07# [- 1.3, - 0.9]
Change from baseline [b, d]	0.39 [0.22, 0.56]	- 0.74 [- 0.87, - 0.62]
Difference from placebo [b, d]	-	- 1.18# [- 1.39, - 0.98]

a: mean ± standard deviation

b: least squares mean

c: at 16 weeks from the start of the administration

d: at the end of treatment period

#: p < 0.001 (unrestricted LSD method using the baseline value as a covariate), 2-sided 95% confidence interval shown in [ ]

In patients who were administered with Luseogliflozin (Luseco) continuously for 52 weeks as the result of assignment in the Luseogliflozin (Luseco) 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 hypoglycemia as an adverse drug reaction was 29.6% (47/159 subjects) in the 52 weeks administration group.

(3) Long-term study of Luseogliflozin (Luseco) in add-on combination with GLP-1 receptor agonists

To patients with type 2 diabetes mellitus whose plasma control was insufficiently controlled by diet and exercise therapies and GLP-1 receptor agonists alone (76 subjects), 2.5 mg or 5 mg (when the dose was increased) of luseogliflozin was orally administered once daily before breakfast for 52 weeks. The results were as the following table. The incidence of hypoglycemia as an adverse drug reaction was 6.6% (5/76 subjects).

Table 6. Results of long-term study of Luseogliflozin (Luseco) in add-on combination with GLP-1 receptor agonists

Concomitant drugs	N	HbA1c (NGSP value) (%)	
		Baseline [a]	Change from baseline at Week 52 [b]
GLP-1 receptor agonists	76	8.52 ± 1.08	- 0.68 [- 0.9, - 0.5]

a: mean ± standard deviation

b: mean, 2-sided 95% confidence interval shown in [ ]

Efficacy in patients with renal impairment

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.

Table 7. Results at Week 24 of double-blind placebo-controlled study in type 2 diabetic patients with moderate renal impairment

	Efficacy in Patients with Renal Impairment	
	Placebo	Luseogliflozin (Luseco) 2.5 mg
N	50	95
HbA1c (NGSP value) (%)		
Baseline [a]	7.69 ± 0.65	7.72 ± 0.68
Change from baseline [b]	0.09 [- 0.1, 0.3]	- 0.11 [- 0.2, 0.0]
Difference from placebo [b]	-	- 0.19# [- 0.4, 0.0]

a: mean ± standard deviation

b: least squares mean

#: p < 0.05 (unrestricted LSD method using the baseline value as a covariate), 2-sided 95% confidence interval shown in [ ]

When, in addition to the above administration, 2.5 mg or

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

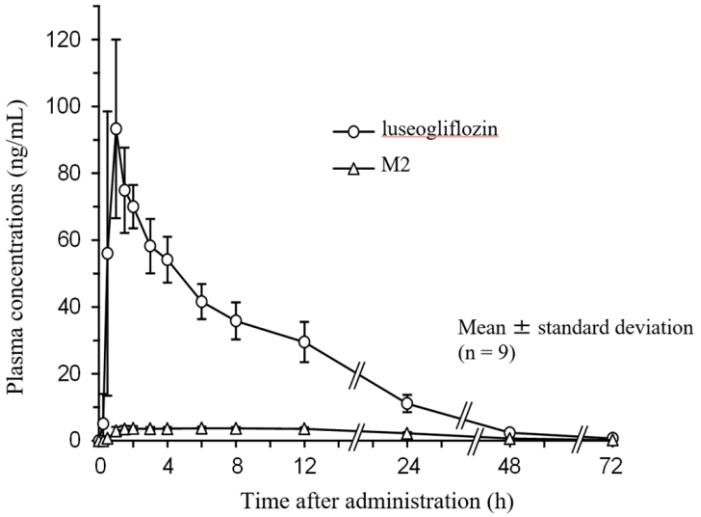
5 mg (when the dose was increased) of luseogliflozin was administered once daily for 28 weeks (52 weeks in total) (95 subjects) (HbA1c [NGSP value] at the start of the administration: 7.72% ± 0.68%), change from the start of the administration in HbA1c (NGSP value) (mean [2-sided 95% confidence interval])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

5.2 Pharmacokinetic properties

Plasma Concentrations

Single administration

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.



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

Repeat administration

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.

Mean ± standard deviation

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

Effects of food intake

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.

Protein Binding

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

Metabolism

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).

Excretion

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*).

Special populations

Patients with Renal Impairment

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

Patients with Hepatic Impairment

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

Elderly Patients

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.

Paediatric population

Pharmacokinetics in the paediatric population have not been studied.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, 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_{0-24h} values of luseogliflozin at this dose were 21 to 48 times higher than the AUC_{τ} 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_{0-24h} 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_{τ} 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 were 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_{τ} value in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose hydrate
Microcrystalline cellulose
Sodium starch glycolate
Hydroxypropylcellulose
Magnesium stearate
Hypromellose
Titanium oxide
Macrogol 400
Carnauba wax
Light anhydrous silicic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Tablets of
2.5 mg:Polypropylene Film/Aluminum Foil Blister Pack x 10's in Aluminum Bag (Box of 100's)
5 mg: Polypropylene Film/Aluminum Foil Blister Pack x 10's in Aluminum Bag (Box of 100's)

6.6 Caution

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

6.7 Special precautions for disposal

No special requirements.

6.8 Storage

Store at temperatures not exceeding 30°C.

7. MARKETING AUTHORISATION HOLDER

Under Authority of:
Taisho Pharmaceutical Co., Ltd.
3-24-1 Takada, Toshima-ku, Tokyo, Japan

Manufactured by:
Taisho Pharmaceutical Co., Ltd. Omiya Factory
403, Yoshino-cho 1-chome, Kita-ku, Saitama-shi, Saitama 331-9520 Japan

Imported by:
Taisho Pharmaceuticals (Philippines), Inc.
8th Floor CLIPP Center Building
11th Ave. cor. 39th St., Bonifacio Global City
Taguig, Philippines

8. MARKETING AUTHORISATION NUMBER(S)

Luseogliflozin (Luseco) 2.5 mg film-coated tablet:
DR-XY47725
Luseogliflozin (Luseco) 5 mg film-coated tablet:
DR-XY47724

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 February 2022

10. DATE OF REVISION OF THE TEXT

19 April 2022