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Report on Investigation Results

August, 21, 2019

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Branded name]	Zafatek Tablets 25 mg, 50mg, 100 mg
[Non-proprietary name]	Trelagliptin succinate
[Approval holder]	Takeda Pharmaceutical Company Limited.
[Indications]	Type 2 diabetes mellitus
[Dosage and administration]	The usual adult dosage is 100 mg of trelagliptin orally administered once weekly.
[Investigating office]	Office of Pharmacovigilance I

II. Investigation background

Zafatek Tablets (hereinafter referred to as “Zafatek”) 50 mg and 100 mg is an oral hypoglycemic agent that inhibits dipeptidyl peptidase-4 (hereinafter “DPP-4”) and is administered once weekly. Zafatek was approved for marketing with an indication for “type 2 diabetes mellitus” in March, 2015 in Japan.

In the clinical pharmacology study of Zafatek 50 mg and 100 mg (101 Study) conducted up to the products’ application for marketing, the plasma concentration-area under the concentration curve (hereinafter, “AUC”) of unchanged trelagliptin after a single dose of Zafatek at 50 mg was 3.01 fold and 3.68 fold in patients with severe renal impairment and end stage renal failure, respectively, in comparison to that of patients with normal renal function. Based on this result, the marketing authorization holder (hereinafter, MAH) contraindicates “patients with severe renal impairment or end stage renal failure on dialysis” for Zafatek based on the Pharmaceuticals and Medical Devices Agency’s (hereinafter, PMDA) conclusion in the review of this application that “PMDA accepted the applicant's explanation that at present, trelagliptin should be contraindicated in patients with severe renal impairment and patients with end stage renal failure because (1) the safety of trelagliptin, which is a renally excreted drug, has not been determined in these patient populations who

have a risk of elevated blood trelagliptin concentrations since no lower dosage strength is proposed for use in patients with high exposure, and (2) trelagliptin is a once-weekly oral hypoglycemic agent with sustained glucose-lowering effects"[1].

Later the MAH conducted a clinical study (hereinafter, "SYR-472-3003 Study") to examine the efficacy and safety of Zafatek 25 mg once weekly in patients with type 2 diabetes mellitus complicated with severe renal impairment or end stage renal failure. The MAH obtained its results, then applied for marketing approval of Zafatek 25 mg recently. Under the circumstances, the applicant requested Ministry of Labour, Health and Welfare that the contraindication should exclude "patients with severe renal impairment or end stage renal failure on dialysis" for the product. PMDA conducted this investigation based on "Investigation regarding Administration of Trelagliptin Succinate to Patients with Severe Renal Impairment or End Stage Renal Failure" (PSEHB/PSD Notification No.0704-1 by the Director, Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated July 4, 2019) which was issued by Ministry of Health, Labour and Welfare in response to the request. Whereas Zafatek 25 mg was approved for marketing on August 21, 2019.

PMDA has held an Expert Discussion as part of the investigation. The expert advisors for the Expert Discussion were nominated based on their declarations, concerning this product, in accordance with the provisions of "Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8 dated December 25, 2008).

III. Summary of documents submitted by the marketing authorization holder

1. A phase III clinical study in patients with type 2 diabetes mellitus complicated by severe renal impairment or end stage renal failure (SYR-472-3003 Study)

A clinical study that covered a double-blinded phase (a placebo-controlled, randomized, double-blind, parallel-group study) and an open-label phase (an open-label long-term administration study) was conducted at 51 institutions in Japan to examine the efficacy and safety of Zafatek 25 mg once weekly in[2] type 2 diabetes mellitus patients who concomitantly

[1] Excerpt from Review Report for Zafatek Tablets dated on January 13, 2015g
[2] The SYR-472-3003 Study only included the patients who were determined by the principal/sub-investigators to have undergone hemodialysis for more than 6 months prior to giving consent and to be clinically stable among patients with end-stage renal failure.

had[3] severe renal impairment (Creatinine clearance (hereinafter, Ccr) was below 30 mL/min at the start of the observational period without hemodialysis or peritoneal dialysis) or end stage renal failure (with hemodialysis) (the target sample size: 53 patients per group, 106 patients in total) (Figure 1).

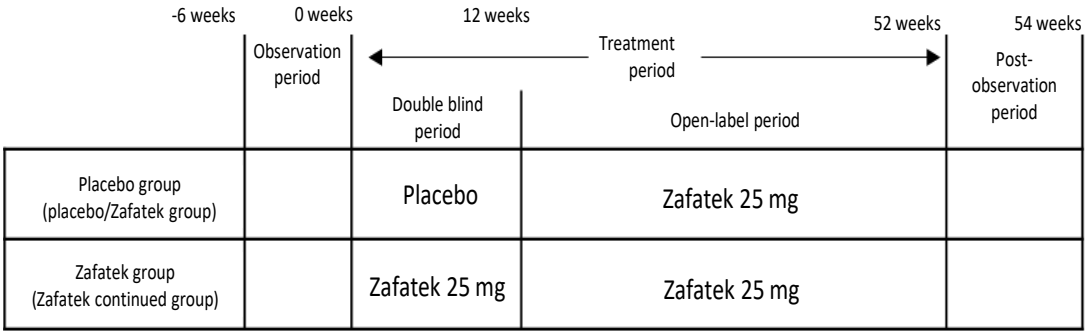

Figure 1 Outline of Study Design

The study period consists of an observation period (6 weeks), treatment period (double-blind period for 12 weeks, open-label period for 40 weeks, 52 weeks in total), and follow-up period (2 weeks).

For dosage and administration, the subjects received a placebo or Zafatek 25 mg (hereinafter, “the placebo group” and “the Zafatek group,” respectively) orally before breakfast once weekly in the double-blind period, and Zafatek 25 mg orally before breakfast once weekly in the open-label period (hereinafter, the patients who switched from the placebo group or the Zafatek group are referred to as “placebo/Zafatek group” and the “Zafatek continued group,” respectively).

For concomitant use of antidiabetic drugs, the dosage and administration of oral hypoglycemic drugs were not to be changed, discontinued, or suspended in the observation and double-blind periods but were allowed to be changed, discontinued, or suspended in the open-label and follow-up periods. If no antidiabetic drugs were concomitantly used in the

[3] Major inclusion criteria
- Type 2 diabetes patients aged 20 years old or older (when giving consent)
- Patients with severe renal impairment or end-stage renal failure
- For 6 weeks or longer prior to the start of the observations period, the patients: (1) have not used antidiabetic drugs (including insulin agents), (2) have used an oral hypoglycemic drug (any of mitiglinide calcium hydrate, repaglinide, acarbose, miglitol, or voglibose) at a certain dosage and administration, or (3) have used an insulin agent [any of mixed type (which contains 30% or less of rapid-acting insulin or very rapid-acting insulin), intermediate type, or long-acting solution type] at a certain dosage and administration.

double-blind period (i.e., if the subjects received the placebo or Zafatek only), an oral hypoglycemic drug was allowed to be added at Week 16 of treatment and beyond. Insulin agents in that kind were not allowed to be changed throughout the study period. The dosage and administration of insulin agents were not allowed to be changed in the observation period, but the change was allowed when [4]the criteria to decrease or increase the dose[5] of insulin agents were satisfied, although it was basically not to be changed, in the double-blind period. Changes in the dosage and administration of insulin agents were allowed when the relevant criteria were satisfied in the open-label and follow-up periods.

All of the randomized 107 subjects (55 subjects in the Zafatek group and 52 subjects in the placebo group) were included in the safety analysis set and the full analysis set (hereinafter, “FAS”). The FAS was subjected to analysis for the primary efficacy and pharmacokinetics. Of the 107 subjects in the safety analysis set, 28 subjects had severe renal impairment (15 in the Zafatek group and 13 in the placebo group) and 79 subjects had end stage renal failure (40 in the Zafatek group and 39 in the placebo group). Ccr (mean ± standard deviation (SD)) at baseline (at the completion of observation period) of patients in the safety analysis set was 23.3 ± 6.55 mL/min in patients with severe renal impairment and 6.6 ± 2.10 mL/min in patients with end stage renal failure.

For the efficacy, changes in HbA1c from baseline, which was the primary endpoint (at the end of observation period) to Week 12 of treatment (at the end of double-blind period), the primary endpoint, were as shown in Table 1, indicating the superiority in the Zafatek group to the placebo group (two-sided significance level 5%, $p<0.0001$; comparison based on the covariate analysis model with factors of HbA1c at baseline and the treatment groups).

[4] Criteria to decrease the dose of insulin agents: When either the following [1] or [2] is satisfied: Of note, a daily dose was allowed to be decreased up to 4 units at the start of the observation period in the double-blind period.
(1) When hypoglycemic symptoms were observed and the principal (sub-) investigator determined the subject to decrease the dose of insulin agents in terms of safety.
(2) The self-measured blood glucose levels were 70 mg/dL or lower twice in a row and hypoglycemic symptoms were suspected, and thereby the principal (sub-) investigator determined the subject to be at a higher risk of developing hypoglycaemia.

[5] Criteria to increase the dose of insulin agents: The self-measured blood glucose levels exceeded 240 mg/dL (in the double-blind period) or 200 mg/dL (in open-label and follow-up periods) twice in a row, and thereby the principal (sub-) investigator determined the subject to increase the dose of insulin agents in terms of safety. Of note, a daily dose was allowed to be increased up to 4 units at the start of the observation period in the double-blind period.

Table 1 Change in HbA1c levels from baseline (at the end of observation period) to Week 12 of treatment (at the end of double-blind period) (FAS)

Treatment group	Baseline (At the end of observation period)	At Week 12 of treatment [a)] (At the end of double-blind period)	Change from baseline [b)]	Between-group difference from the placebo group [b)] [95% Confidence Interval]
Zafatek group (55 patients)	7.57 ± 0. 85	6.87 ± 0.75	-0.71 ± 0. 09	-0.72 [-0.97, -0.47]
Placebo group (52 patients)	7.74 ± 1. 05	7.74 ± 1.31	0. 01 ± 0. 09	

Unit: %, the number of subjects for assessment is provided in parentheses.
Value at each point: Mean ± SD, difference: adjusted mean ± SE, between-group difference: Adjusted mean.
a) The closest data to Day 7 from the last treatment day in the double-blind period were adopted.
b) Covariate analysis model with factors of HbA1c at baseline and the treatment groups.

The difference between the Zafatek and placebo groups of the change specific to renal function in HbA1c levels from baseline (at the end of observation period) to Week 12 of treatment (at the end of double-blind period) [two-sided 95% confidence interval] was - 0.78 [-1.193, -0.367] % in the Zafatek and placebo groups, respectively for patients with severe renal impairment and - 0.67 [-0.982, -0.366] % for patients with end stage renal failure.

The difference of change in HbA1c levels from baseline (at the end of observation period) to Week 24 of treatment (at the end of double-blind period) [two-sided 95% confidence interval] had been - 0.56 [-0.753, -0.367] % in the phase III study conducted to examine the efficacy and safety of Zafatek 100 mg once weekly in Japanese patients with type 2 diabetes mellitus[6] (a placebo/active-controlled, randomized, double-blind, parallel-group study (CCT-002 Study): The approval review data for marketing of Zafatek 50 mg, 100 mg).

Figure 2 shows the changes in HbA1c levels from baseline (at the end of observation period) to Week 52 of treatment (at the end of open-label period). The change in HbA1c level (mean ± SD) at Week 52 of treatment was -0.76 ± 0.824% in the Zafatek-continued group and -0.74 ± 0.843% in the placebo/Zafatek group.

[6] Patients with severe renal impairment or renal failure (for example, patients with Ccr < 30mL/min at the start of observation period)

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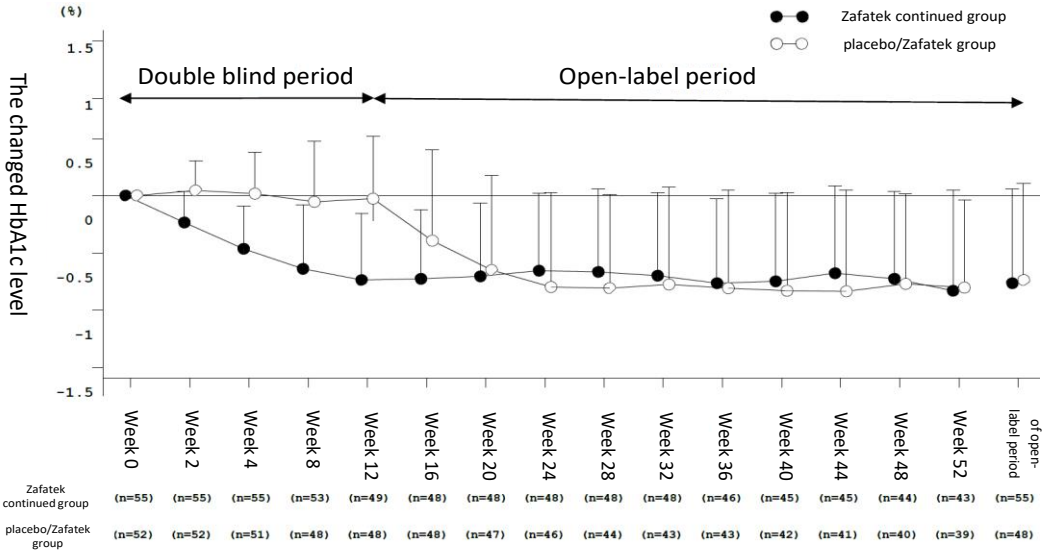

Figure 2 Change in HbA1c levels from baseline (at the end of observation period) to Week 52 of treatment (at the end of open-label period) (FAS, mean + SD)

The change in HbA1c levels (mean ± SD) from baseline (at the end of observation period) to Week 52 of treatment (at the end of open-label period) specific to renal function was -0.69 ± 0.489% in the Zafatek-continued group and -0.80 ± 0.940% in the placebo/Zafatek group for patients with severe renal impairment while the change was -0.79 ± 0.923% in the Zafatek-continued group and -0.72 ± 0.824% in the placebo/Zafatek group for patients with end stage renal failure.

For the pharmacokinetics, the plasma concentrations[7] of the unchanged drug in the Zafatek group at Week 4 and Week 12 of treatment are as provided in Table 2.

[7] Measurement was performed prior to administration when the assessment time and the day of administration were the same.

Table 2 Plasma concentrations of unchanged drug in the Zafatek group at Week 4 and Week 12 of treatment (FAS)

At assessment	Zafatek group		
	The whole	Patients with severe renal impairment	Patients with end stage renal failure
At Week 4 of treatment	20.00 ± 12.18 (54 subjects)	10.12 ± 3.92 (14 subjects)	23.46 ± 12.22 (40 subjects)
At Week 12 of treatment (At the end of double-blind period)	21.60 ± 12.95 (49 subjects)	11.94 ± 8.00 (13 subjects)	25.09 ± 12.68 (36 subjects)

Unit: ng/mL, mean ± SD, the number of subjects for assessment is provided in parentheses.

For the safety profile, the incidence of the adverse events that occurred in the double-blind period and the adverse events whose causality with Zafatek or placebo (hereinafter the investigational drug) cannot be ruled out (hereinafter, “adverse reaction”) was 72.7% (40/55 subjects) and 18.2% (10/55) in the Zafatek group and 61.5% (32/52) and 7.7% (4/52) in the placebo group, respectively. Table 3 shows the adverse events and adverse reactions that occurred in ≥ 5% of subjects in either of the groups.

Table 3 Onset status of adverse events and adverse reactions that occurred in ≥ 5% of subjects in either of the groups during the double-blind period.

Name of event (PT)	Zafatek group (55 patients)		Placebo group (52 patients)	
	Adverse event	Adverse reaction	Adverse event	Adverse reaction
All events	40 (72.7)	10 (18.2)	32 (61.5)	4 (7.7)
Nasopharyngitis	15 (27.3)	0 (0)	5 (9.6)	0 (0)
Contusion	4 (7.3)	0 (0)	3 (5.8)	0 (0)
Fall	4 (7.3)	0 (0)	3 (5.8)	0 (0)
Hypoglycaemia	8 (14.5)	7 (12.7)	4 (7.7)	3 (5.8)
Hyperkalaemia	0 (0)	0 (0)	3 (5.8)	0 (0)
Muscle spasms	0 (0)	0 (0)	4 (7.7)	0 (0)
Headache	3 (5.5)	0 (0)	1 (1.9)	0 (0)

Number of patients with events (incidence %), MedDRA/J (ver.21.0), PT: Preferred Term

Adverse events with an incidence higher by ≥ 5% in the Zafatek group compared to the placebo group were nasopharyngitis (27.3%) and hypoglycaemia (14.5%), both of which were[8] mild or moderate, with no severe events observed.

[8] Mild: Temporary and easy to endure; Moderate: Disrupting everyday activities; Severe: Inhibiting everyday activities

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The incidence of adverse events and adverse reactions during the treatment period (52 weeks, with the double-blind period and open-label period combined) and the follow-up period in the Zafatek-continued group reached 98.2% (54/55 subjects) and 23.6% (13/55), respectively. The adverse reactions observed include hypoglycaemia in 10 subjects (18.2%), atrial fibrillation, ventricular extrasystoles, electrocardiogram prolonged QT, lipase increased, hypocalcaemia, hypoglycaemia unawareness, and hypoaesthesia in 1 subject each (1.8%). There were serious adverse events observed in 23 patients (41.8%) (cataract and diabetic retinopathy in 3 patients each (5.5%), fall, shunt occlusion, and chronic kidney disease in 2 patients each (3.6%), angina pectoris, acute coronary syndrome, acute myocardial infarction, coronary artery stenosis, gastrointestinal necrosis, cholecystitis, pneumonia, diverticulitis, sepsis, shunt stenosis, femoral neck fracture, shunt malfunction, vascular access malfunction, fluid overload, osteoarthritis, pain in extremity, colon adenoma, colon cancer, loss of consciousness, peripheral arterial occlusive disease, and subclavian vein stenosis in 1 patient each (1.8%). The causality with the investigational drug was ruled out for all the events.

The adverse events that resulted in drug discontinuation were observed in 7 patients in the Zafatek-continued group (12.7%) (diverticulitis, sepsis, fall, femoral neck fracture, electrocardiogram prolonged QT, hypoglycaemia, hypoaesthesia, delirium, chronic kidney disease, and renal impairment in 1 patient each (1.8%)). There were no adverse events that resulted in drug discontinuation in 2 subjects or more. There were no adverse events resulting in death.

The incidence of adverse events and adverse reactions during the treatment period (40-week open-label period) and the follow-up period in the placebo/Zafatek group was 100% (48/48 subjects) and 12.5% (6/48), respectively. The observed adverse reactions include hypoglycaemia in 5 subjects (10.4%), electrocardiogram prolonged QT in 2 (4.2%), and altered state of consciousness in 1 (2.1%). The adverse events that resulted in drug discontinuation were observed in 5 patients (10.4%) (including vomiting, cholangitis acute, cholangitis infective, electrocardiogram prolonged QT, altered state of consciousness, myelopathy, and skin ulcer in 1 subject each (2.1%)). There were no adverse events that resulted in drug discontinuation in 2 subjects or more. There were serious adverse events observed in 16 patients (33.3%) (angina pectoris, atrioventricular block complete, coronary artery occlusion, sudden hearing loss, gastrooesophageal reflux disease, large intestine

polyp, vomiting, oedema peripheral, vascular stent stenosis, cholangitis acute, anaphylactic shock, pneumonia, cholangitis infective, shunt stenosis, fluid overload, lumbar spinal stenosis, loss of consciousness, myelopathy, dementia with Lewy bodies, diabetic nephropathy, sleep apnoea syndrome, skin ulcer, and peripheral arterial occlusive disease in 1 patient each (2.1%) The causality with the investigational drug was ruled out for all the events. There were no adverse events resulting in death.

Adverse events related to renal impairment were specified as adverse events of special interest in consideration of the risks set in the risk management plan for Zafatek and the subjects of this study as shown in Table 4.

Table 4　Definition of adverse events of special interest

Adverse events of special interest	Definition
Adverse events related to hypoglycaemia	Events (PT) that involve “hypoglycaemia”
Adverse events related to skin disorders	Events (PT) categorized into SOC “Skin and subcutaneous tissue disorders”
Adverse events related to acute pancreatitis	Events (PT) retrieved from SMQ “acute pancreatitis” in narrow search, or events (PT) that are categorized into SMQ “acute pancreatitis” in broad search and related to laboratory test results (blood/urine analysis)
Adverse events related to arrhythmia associated with QT/QTc interval prolongation	Torsades de Pointes, sudden death, cardiac death, sudden cardiac death, cardiac arrest, cardio-respiratory arrest, ventricular tachycardia, ventricular tachyarrhythmia, ventricular arrhythmia, ventricular fibrillation, cardiac fibrillation, ventricular flutter, altered state of consciousness, syncope, loss of consciousness, convulsion, epilepsy, electrocardiogram prolonged QT, Long QT syndrome, Long QT syndrome congenital, electrocardiogram abnormal QT prolongation, electrocardiogram repolarisation abnormality, and electrocardiogram abnormal U wave (all are PT).
Adverse events related to intestinal obstruction	Events (PT) retrieved from SMQ “gastrointestinal obstruction” in narrow search
Adverse events related to infection	Adverse events (PT) categorized into SOC “Infections and infestations”
Adverse events related to malignant tumors	Adverse events (PT) categorized into SOC “Neoplasms benign, malignant and unspecified (including cysts and polyps)”
Adverse events related to hypersensitivity	Events (PT) retrieved from SMQ “hypersensitivity” in narrow search, or events (PT) that are categorized into SMQ “angioedema” in narrow search and not into SOC “Skin and subcutaneous tissue disorders”

Adverse events of special interest	Definition
Cardiovascular adverse events	Events (PT) retrieved from SMQ “myocardial infarction” in broad search, or events (PT) that are categorized into SMQ “central nervous system haemorrhages and cerebrovascular conditions” in broad search
Adverse events related to pemphigoid	Pemphigoid, ocular pemphigoid (both are PTs)
Adverse events related to renal impairment	Adverse events (PT) categorized into HLGT “nephropathies” or “renal disorders (excl nephropathies),” or HLT “renal function analyses.” Not including urinary system diseases and kidney stone.

MedDRA/J(ver.21.0)
SMQ: Standard MedDRA Queries, SOC: System Organ Class, HLGT: High Level Group Term, HLT: High Level Term

Table 5 provides the incidence of adverse events of special interest in the double-blind period and the treatment/follow-up period. The events whose incidence was higher by ≥ 5% in the Zafatek group than in the placebo group were events related to hypoglycaemia and events related to infection.

Table 5 Summary of adverse events of special interest that occurred in the double-blind, and treatment/follow-up periods

Name of event	Number of patients (%)			
	Double-blind period		Treatment/ follow-up period [a)]	
	Zafatek group (55 patients)	Placebo group (52 patients)	Zafatek-continued group (55 patients)	Placebo/Zafatek group (48 patients)
Adverse events related to hypoglycaemia	9 (16.4)	4 (7.7)	13 (23.6)	7 (14.6)
Adverse events related to skin disorders	4 (7.3)	5 (9.6)	15 (27.3)	16 (33.3)
Adverse events related to acute pancreatitis	2 (3.6)	1 (1.9)	2 (3.6)	0 (0)
Adverse events related to arrhythmia associated with QT/QTc interval prolongation	1 (1.8)	4 (7.7)	4 (7.3)	5 (10.4)
Adverse events related to intestinal obstruction	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events related to infection	17 (30.9)	10 (19.2)	32 (58.2)	27 (56.3)

Name of event	Number of patients (%)			
	Double-blind period		Treatment/ follow-up period [a)]	
	Zafatek group (55 patients)	Placebo group (52 patients)	Zafatek-continued group (55 patients)	Placebo/Zafatek group (48 patients)
Adverse events related to malignant tumors	0 (0)	0 (0)	3 (5.5)	1 (2.1)
Adverse events related to hypersensitivity	0 (0)	1 (1.9)	1 (1.8)	5 (10.4)
Cardiovascular adverse events	2 (3.6)	1 (1.9)	3 (5.5)	2 (4.2)
Adverse events related to pemphigoid	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events related to renal impairment	1 (1.8)	3 (5.8)	5 (9.1)	3 (6.3)

Number of patients with events (incidence %), MedDRA/J (ver.21.0)

a) Treatment period (for 52 weeks in total with double-blind period and open-label period) and follow-up period for the Zafatek group, and treatment period (for 40 weeks of open-label period) and follow-up period for the placebo/Zafatek group

The events related to hypoglycaemia observed in the Zafatek-continued group (23.6% (13/55 subjects)) were all hypoglycaemia except hypoglycaemia unawareness in 1 subject, all of which were mild in severity. The events related to hypoglycaemia observed in the placebo/Zafatek group (14.6% (7/48 subjects) were hypoglycaemia, all of which were mild in severity. The adverse events related to infection observed in the Zafatek-continued group (58.2% (32/55 subjects) that occurred in ≥ 5% of the subjects include nasopharyngitis at 43.6% (24/55). The severity of the events was ‘severe’ for diverticulitis and sepsis in 1 subject each (1.8%), ‘moderate’ for nasopharyngitis, diverticulitis, and pneumonia in 1 subject each (1.8%). The rest of the events were all ‘mild’. The adverse events related to infection observed in the placebo/Zafatek group (56.3% (27/48 subjects)) that occurred in ≥ 5% of the subjects include nasopharyngitis at 33.3% (16/48) and influenza at 8.3% (4/48). The severity of the events was ‘severe’ for cholangitis infective in 1 subject (2.1%), ‘moderate’ for influenza, pneumonia, subcutaneous abscess, and urinary tract infection in 1 subject each (2.1%), and the rest of the events were all ‘mild’. The causality between Zafatek and the events related to infection observed in the Zafatek-continued group and in the placebo/Zafatek group was ruled out.

The adverse events of special interest which showed a difference in the incidence between the subjects with severe renal impairment and the subjects with end stage renal failure were

the events related to hypoglycaemia and the events related to infection in the double-blind period, and the events related to infection and the events related to renal functions in the treatment and follow-up periods.

The incidence of events related to hypoglycaemia was 26.7% (4/15 subjects) in the subjects with severe renal impairment and 12.5% (5/40) in the subjects with end stage renal failure of the Zafatek group during the double-blind period. The incidence of events related to infection was 26.7% (4/15 subjects) in the subjects with severe renal impairment and 32.5% (13/40) in the subjects with end stage renal failure in the Zafatek group during the double-blind period. The incidence in the subjects of the Zafatek-continued group and the Zafatek/placebo group combined reached 42.3% (11/26 subjects) in the subjects with severe renal impairment and 62.3% (48/77) in the subjects with end stage renal failure during the treatment and follow-up periods. The incidence of events related to renal functions in the subjects of the Zafatek-continued group and the Zafatek/placebo group combined reached 23.1% (6/26 subjects) in the subjects with severe renal impairment and 2.6% (2/77) of the subjects with end stage renal failure during the treatment and follow-up periods. The events related to renal functions that occurred in at least 2 subjects include chronic kidney disease in 3 subjects (11.5%), and nephrogenic anaemia and renal impairment in 2 subjects each (7.7%), all of which were observed in subjects with severe renal impairment. The events related to renal functions observed in either group were mild or moderate in severity, and the causality with Zafatek was denied in all of them.

2. Spontaneous reports for patients complicated with renal impairment in Japan

The MAH selected the subjects complicated with renal impairment[9] among those in adverse reaction reports of Zafatek (serious cases, non-serious cases) collected for the spontaneous report in Japan from the launch on May 28, 2015 to February 20, 2019. As a result, a total of 32 patients were extracted including only 1 patient with severe renal impairment as a case with severe renal impairment or end stage renal failure. The patient[10] with severe renal impairment developed serious hypoglycaemia while receiving

[9] Cases for which the complication's column in the adverse reaction case reports includes the following (1) to (3): (1) HLGT "nephropathies" or "renal disorders (excl nephropathies)," or HLT "renal function analyses" excluding congenital renal diseases experienced prior to the start of Zafatek, (2) PTs that are categorized into HLT "Renal therapeutic procedures" and include "dialysis," (3) therapeutic procedures for renal impairment (hemofiltration, etc.).

[10] This is a case where the assigned physician described that the patient had been under severe decreased renal function as his/her opinion in the adverse reaction case report, and the renal function test results were unknown when Zafatek was started.

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both Zafatek 50 mg and a high dose of sulfonylurea, and thereby the effect of the concomitant drug on the onset of hypoglycaemia could not be ruled out.

3. Special drug use-results survey (a survey for long-term administration)

A special drug use-results survey in type 2 diabetes mellitus patients including those with mild to moderate renal impairment (the observation period: 3 years; target sample size: 3000 patients) is ongoing during the survey period between May 2016 and October 2021. The safety profile of the drug was examined in 1258 patients included for the safety analysis by the renal function level as of March 25, 2019 in this special drug use-results survey.

Of the patients for the safety analysis, there were 730 patients with normal renal function or mild renal impairment (Ccr: ≥50 (mL/min)) (hereinafter, “patients with mild renal impairment, etc.”), 107 patients with moderate renal impairment (Ccr: ≥30 and <50), and 3 patients with severe renal impairment (Ccr: <30).

The incidence of adverse events and adverse reactions was 5.1% (37/730 patients) and 2.7% (20/730), respectively, in patients with mild renal impairment, etc., 6.5% (7/107) and 1.9% (2/107), respectively, in patients with moderate renal impairment, and 0% (0/3) for both in patients with severe renal impairment. The incidence of serious adverse events and serious adverse reactions was 0.96% (7/730 patients) and 0.27% (2/730), respectively, in patients with mild renal impairment, etc., 3.74% (4/107) and 0% (0/107), respectively, in patients with moderate renal impairment, and 0% (0/3) for both in patients with severe renal impairment. The serious adverse events observed in patients with moderate renal impairment include pneumonia, asthma/cardiac failure, ureterolithiasis/postrenal failure, and sudden death in 1 patient each (0.93%). The causality of all the events with Zafatek was ruled out. For adverse events and adverse reactions, there was no tendency for the renal function level to increase the incidence of adverse events and adverse reactions.

4. A clinical pharmacology study in patients with renal impairment (101 Study: Reference material in marketing approval application of Zafatek 50 mg, 100 mg)

In a clinical pharmacology study in non-Japanese male and female adults to examine the single-dose effect of Zafatek at 50 mg on the renal function pharmacologically and pharmacokinetically, the hemodialysis effect on the pharmacokinetic of Zafatek was examined. The mean Zafatek dose eliminated in 4-hour hemodialysis (in 4 subjects) was

9.2% of the administered dose (coefficient of variation 5.8%).

IV. PMDA Investigation

1. Investigation results of pharmacokinetic, efficacy, and safety

PMDA conducted an investigation as mentioned below in view of the pharmacokinetics, efficacy, and safety regarding whether the language “patients with severe renal impairment or patients with end stage renal failure on dialysis” should be deleted in the Contraindications section.

1-1. Pharmacokinetics of Zafatek in patients with severe renal impairment and patients with end stage renal failure

The MAH explained as follows about the exposure when Zafatek 25 mg was administered once weekly to patients with severe renal impairment and patients with end stage renal failure:

The exposure of Zafatek at steady state when administered at 25 mg once weekly in patients with severe renal impairment or patients with end stage renal failure was estimated by using an existing population pharmacokinetics model based on data of 3 studies conducted in Japan up to marketing approval of Zafatek 50 mg and 100 mg (a phase I single-dose study (CPH-001 Study), a phase II dose-finding study (CCT-001 Study), and a phase III long-term monotherapy or concomitant use study (OCT-001 Study)). (Table 6)

Table 6 Estimated C_{max} and $AUC_{0\text{-}168\ h}$ [a)] of unchanged drug at steady state when Zafatek was administered at 100 mg orally once weekly to patients with normal renal functions and at 25 mg orally once weekly to patients with severe renal impairment or patients with end stage renal failure.

Renal impairment level (Ccr [b)])	Dosage (mg)	C_{max} (ng/mL)	$AUC_{0\text{-}168\ h}$ (ng·h/mL)
Patients with normal renal functions (104.64 mL/min)	100	536	6972
Patients with severe renal impairment (22 mL/min)	25	143	4172
Patients with end stage renal failure (6 mL/min)	25	158	8000

a) Estimated Ccr presented in parentheses
b) Ccr in patients with normal renal functions: The median Ccr at the population pharmacokinetic analysis, Ccr in patients with severe renal impairment or patients with end stage renal failure: The median Ccr in each group of SYR-472-3003 Study.

As a result of estimation using the population pharmacokinetic model, a lower estimated C_{max} level at steady state was obtained when Zafatek 25 mg was administered to patients with severe renal impairment or patients with end stage renal failure in comparison to the level when it was administered 100 mg to patients with normal renal functions (26.7% and 29.5%, respectively). The estimated $AUC_{0\text{-}168\ h}$ at steady state when Zafatek 25 mg was administered to patients with severe renal impairment or patients with end stage renal failure was lower (59.8%) in patients with severe renal impairment and similar (114.7%) in patients with end stage renal failure.

PMDA considers that the appropriateness to administer Zafatek 25 mg once weekly to patients with severe renal impairment and patients with end stage renal failure should be determined based on its efficacy and safety as well as its pharmacokinetics, as the exposure of Zafatek in steady state in the group of normal renal function with Zafatek 100 mg orally once weekly is different from that in the group of severe renal impairment or end stage renal failure with Zafatek 25 mg orally once weekly, which was estimated by the population pharmacokinetic model.

1-2. Efficacy when Zafatek 25 mg was administered to patients with severe renal impairment and patients with end stage renal failure

PMDA considers that efficacy was appropriately demonstrated from the administration of Zafatek 25 mg once weekly to patients with severe renal impairment and patients with end stage renal failure based on the following results obtained from SYR-472-3003 Study:

- For change in HbA1c level, the primary endpoint in the double-blind period, the superiority of the Zafatek group to the placebo group was confirmed.
- The HbA1c level decreased from baseline in the Zafatek-continued group was maintained for 52 weeks including the open-label period.
- A comparable tendency to that in the overall population was observed in any subgroup of patients with severe renal impairment and patients with end stage renal failure.

The changes in HbA1c in SYR-472-3003 Study during the double-blind period were comparable to those of CCT-002 Study where Zafatek 100 mg was administered once weekly in type 2 diabetes patients without severe renal impairment or renal failure.

1-3. Safety when Zafatek 25 mg was administered to patients with severe renal impairment or with end stage renal failure

PMDA determined that the safety profile is acceptable when Zafatek 25 mg is administered once weekly to patients with severe renal impairment and patients with end stage renal failure based on the following reasons:

- The events related to hypoglycaemia and events related to infection occurred more frequently in the Zafatek group than in the placebo group in SYR-472-3003 Study. However, all the events related to hypoglycaemia were mild, and the causality with Zafatek was ruled out for all the events related to infection including severe cases (diverticulitis and sepsis in 1 case each) and moderate cases (nasopharyngitis, diverticulitis, and pneumonia in 1 case each). There were no clinically significant problems in the safety profile compared to patients with normal renal functions and patients with mild to moderate renal impairment.
- There were no clinically significant differences in the safety profile of patients with severe renal impairment and patients with end stage renal failure in SYR-472-3003 Study.
- Post-marketing safety information on Zafatek available as of today (special drug use-results survey, spontaneous reports in Japan) did not reveal information indicating any significant problems with safety when Zafatek 25 mg is administered once weekly to patients with severe renal impairment and patients with end stage renal failure.

1-4. PMDA's decision based on investigation results

PMDA determined that it would be acceptable to add a statement on the necessity to reduce the dose to 25 mg for patients with severe renal impairment and patients with end stage renal failure and delete "patients with severe renal impairment and patients with end stage renal failure on dialysis" in the Contraindications section because the efficacy of Zafatek 25 mg was confirmed when administered once weekly to patients with severe renal impairment and patients with end stage renal failure and no significant safety concerns were identified.

Of note, the MAH plans to conduct a special drug use-results survey (a survey for long-term use in patients with type 2 diabetes complicated with severe renal impairment or end stage renal failure) with "hypoglycaemia" and "the safety when administered to patients with

renal impairment" as safety specifications for an additional pharmacovigilance activity, following the removal of the language from "patients with severe renal impairment and patients with end stage renal failure on dialysis" in the Contraindications section.

2. Reliability of the documents submitted by the marketing authorization holder

The documents submitted by the MAH are the same as the ones submitted when it applied for approval of Zafatek tablets 25 mg. The documents for approval application were subject to the re-examination compliance paper review and the GCP on-site review. PMDA determined that this investigation could be acceptable to conduct in accordance with the submitted documents, based on these reviews.

3. Expert discussions

3-1. Efficacy when Zafatek 25 mg was administered to patients with severe renal impairment and patients with end stage renal failure

The expert members supported the PMDA's decision that administration of Zafatek 25 mg once weekly to patients with severe renal impairment and patients with end stage renal failure had demonstrated efficacy.

3-2. Safety when Zafatek 25 mg was administered to patients with severe renal impairment and patients with end stage renal failure

The expert members supported the PMDA's decision that administration of Zafatek 25 mg once weekly to patients with severe renal impairment and patients with end stage renal failure had demonstrated an acceptable safety profile.

Meanwhile, some expert advisors gave the following opinions:

- The SYR-472-3003 Study showed a higher incidence of nasopharyngitis in the Zafatek group, which is not a serious adverse event, than in the placebo group. Given that nasopharyngitis is rarely recognized as a drug-induced adverse event as well, careful pharmacovigilance for infection risks is considered necessary when Zafatek 25 mg is administered to patients with severe renal impairment and patients with end stage renal failure.
- Given that most of the adverse reactions observed in the SYR-472-3003 Study were hypoglycaemia and that only 1 patient experienced hypoglycaemia after receiving

Zafatek as monotherapy in the phase III study (CCT-002 Study) and the phase III long-term monotherapy or concomitant use study (OCT-001 Study), which were conducted for Zafatek 50 mg and 100 mg in Japan prior to the marketing approval, hypoglycaemia may be more likely to occur in patients with severe renal impairment or patients with end stage renal failure, and appropriate caution should be issued for hypoglycaemia.

PMDA's opinion is as follows based on the opinions of expert advisors:

A caution should be issued to carefully monitor the condition of patients with severe renal impairment or patients with end stage renal failure while they receive Zafatek 25 mg, and other appropriate precautions should also be given as required by giving special attention to the onset status of hypoglycaemia and infections based on information from not only spontaneous reports but also special drug use-results surveys, research reports, etc.

3-3. Appropriateness of deleting "patients with severe renal impairment or patients with end stage renal failure on dialysis" in the Contraindications

The expert advisors supported the PMDA's decision that it is acceptable to delete "patients with severe renal impairment or patients with end stage renal failure on dialysis" in the Contraindications section in the package insert after stating that the dose should be reduced to 25 mg for patients with severe renal impairment and patients with end stage renal failure.

V. Overall assessment

PMDA determined based on the above consideration that it is acceptable to delete "patients with severe renal impairment or patients with end stage renal failure on dialysis" in the Contraindications section of the package insert of Zafatek after stating precautions that the dose should be reduced to 25 mg for patients with severe renal impairment and patients with end stage renal failure and that the condition of patients should be carefully monitored during treatment, as mentioned in the attached revision draft. Accordingly, PMDA also considered it appropriate to collect information from a special drug use-results survey (a survey for long-term use in patients with type 2 diabetes patients complicated by severe renal impairment or end stage renal failure) on the safety of Zafatek including hypoglycaemia and infections in patients with severe renal impairment and patients with end stage renal failure.

Attachment (revision draft for trelagliptin succinate)

Revision in line with the Instructions for Package Inserts of Prescription Drugs, PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau, MHW, dated April 25, 1997 (Old instructions): Revised language is underlined.

<table>
<tr><th>Current</th><th>Revision (draft)</th></tr>
<tr><td>Contraindications (This drug should not be administered to the following patients.)
(1) to (2) (snip)
(3) Patients with severe renal impairment or patients with end stage renal failure on dialysis [Zafatek is mainly excreted from the kidney, and the blood concentration of Zafatek may increase due to delay in the excretion.] (Refer to the “Pharmacokinetics” section.)
(4) (snip)</td><td>Contraindications (This drug should not be administered to the following patients.)
(1) to (2) (snip)
(deleted)

(3) (snip)</td></tr>
<tr><td>Dosage and Administration
The usual adult dosage is 100 mg of trelagliptin administered orally once weekly.

Precautions concerning Dosage and Administration
(1) Patients with moderate renal impairment should reduce the dose according to the table below as a delay in excretion may increase the blood concentration of this drug. (Refer to the Pharmacokinetics section.)

Dosage for patients with moderate renal impairment
<table>
<tr><th></th><th>Serum creatinine (mg/dL)*</th><th>Creatinine clearance (Ccr, mL/min)</th><th>Dosage</th></tr>
<tr><td>Patients with moderate renal impairment</td><td>Men:1.4 < to ≤ 2.4
Women:1.2 < to ≤ 2.0</td><td>30 ≤ to < 50</td><td>50 mg, once weekly</td></tr>
</table>
*: Converted level equivalent to Ccr (age: 60 years old, body</td><td>Dosage and Administration
The usual adult dosage is 100 mg of trelagliptin administered orally once weekly.

Precautions concerning Dosage and Administration
(1) Patients with moderate or severer renal impairment should reduce the dose according to the table below according to patients’ renal function level, as a delay in excretion may increase the blood concentration of this drug. (Refer to the Pharmacokinetics section.)

Dosage for patients with moderate or severer renal impairment
<table>
<tr><th></th><th>Serum creatinine (mg/dL)*</th><th>Creatinine clearance (Ccr, mL/min)</th><th>Dosage</th></tr>
<tr><td>Patients with moderate renal impairment</td><td>Men:1.4 < to ≤ 2.4, women:1.2 < to ≤ 2.0</td><td>30 ≤ to < 50</td><td>50 mg, once weekly</td></tr>
<tr><td>Patients with severe renal</td><td>Men: > 2.4
Women: > 2.0</td><td>< 30</td><td>25 mg, once</td></tr>
</table></td></tr>
</table>

weight: 65 kg) (2) snip Precautions 1. Careful administration (Zafatek should be administered with care in the following patients) Patients with the following conditions: (1) Patients with moderate renal impairment (Refer to the sections of Precautions concerning Dosage and Administration and Pharmacokinetics.) (2) to (6) snip	<table><tr><td>impairment/patients with end stage renal failure</td><td></td><td></td><td>weekly</td></tr></table> A temporal association between Zafatek and hemodialysis is not considered for patients with end stage renal failure. *: Converted level equivalent to Ccr (age: 60 years old, body weight: 65 kg) (2) snip Precautions 1. Careful administration (Zafatek should be administered with care in the following patients.) Patients with the following conditions: (1) Patients with moderate or severer renal impairment or patients with end stage renal failure on dialysis (The blood concentration of Zafatek may increase, depending on the renal function level. The dosage of Zafatek should be reduced, and the condition of the patient should be carefully monitored.) (Refer to the sections of Precautions concerning Dosage and Administration and Pharmacokinetics.) (2) to (6) snip

<table>
<tr>
<td>Clinical Studies
1. to 2. (snip)
(N/A)</td>
<td>Clinical Studies
1. to 2. (snip)
3. Patients with type 2 diabetes mellitus complicated by severe renal impairment or end stage renal failure (a confirmatory/long-term study)[19)]
(1) Double-blind period
Trelagliptin 25 mg was administered for 12 weeks (before breakfast, once weekly) in patients with type 2 diabetes mellitus complicated with severe renal impairment or end stage renal failure who had poor glycemic control even after dietary therapy or kinesitherapy was introduced, or after fast-acting insulin secretion stimulants, α-glucosidase inhibitor, or insulin agents was administered in addition to dietary therapy or kinesitherapy. The results are provided in the following table: The mean (SD) of HbA1c (NGSP level) at baseline was 7.57 (0.85) % in the trelagliptin 25 mg group and 7.74 (1.05) % in the placebo group.
<table>
<tr><th rowspan="2">Treatment group</th><th colspan="2">HbA1c (NGSP level) (%)</th></tr>
<tr><th>Changed volume from baseline</th><th>Difference from the placebo</th></tr>
<tr><td>Placebo
(n=52)</td><td>0.01 (0.09)</td><td rowspan="2">-0.72[#]
[-0.97, -0.47]</td></tr>
<tr><td>Trelagliptin 25 mg
(n=55)</td><td>-0.71 (0.09)</td></tr>
</table>
The adjusted mean level after being adjusted by HbA1c (NGSP level) at baseline, ( ): SD, [ ]: Two-sided 95% confidence interval
#: p<0.0001 (a test of the difference in the population mean based on an ANCOVA model with HbA1c (NGSP level) at baseline as a covariate)
n: Number of patients in the analysis set

(2) Continued open-label long-term administration period
Stable glycemic control was maintained for 52 weeks in patients who received trelagliptin 25 mg continuously as well as in the patients who switched from placebo to trelagliptin 25 mg after the completion of the double-blind period. The mean change (SD) in HbA1c (NGSP level) from baseline at the end of the continued</td>
</tr>
</table>

	open-label long-term administration period was -0.76 (0.82) % in the trelagliptin 25 mg continued group and -0.74 (0.84) % in the switched group. The incidence of an adverse reaction, hypoglycaemia, up to the end of the continued open-label long-term administration period was 18.2% (10/55 patients) in the trelagliptin 25 mg continued group and 10.4% (5/48) in the switched group.
References 1) to 18) (snip) (N/A)	References 1) to 18) (snip) 19) Clinical studies of trelagliptin (6) (an in-house document) (The reference numbers are moved down thereafter.)

N/A: Not Applicable, because the section is not included in the current package insert.