ZAFATEK®

1. Name of the Medicinal Product

ZAFATEK® (Trelagliptin) 100 mg film-coated tablets

2. Qualitative and Quantitative Composition

Each film-coated tablet contains 100 mg of trelagliptin (as 133 mg of trelagliptin succinate).

For excipients, see section 6.1.

3. Pharmaceutical Form

Light red oval, film-coated tablets with score on both side with "D" and "389" printed on one side.

4. Clinical Particulars

4.1 Therapeutic Indications

ZAFATEK is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

4.2 Posology and Method of Administration

Dosage

Usually, for adults, 100 mg of trelagliptin is orally administered once a week. The score line is not intended for dose adjustment. Do not break or crush the tablet.

Special Patient Populations

Elderly Patients

Since the elderly often have reduced renal function, precautions should be taken against the onset of adverse reactions and careful administration should be performed under close observation (See Impaired Renal Function and sections 4.3 and 5.2).

Pediatric Patients

The safety of trelagliptin tablets in low birth weight infants, neonates, nursing infants, infants and children has not been established (no clinical experience).

Impaired Renal Function

Since blood concentrations of trelagliptin may increase due to a delay in the excretions in patients with moderate renal impairment, the 100 mg dose is not recommended for patients with moderate renal impairement.

Impaired Hepatic Function

No dose adjustments are required for patients with hepatic impairment.

4.3 Contraindications

- Hypersensitivity to trelagliptin or any of its components
- Patients with severe renal impairment or end-stage renal failure on dialysis

4.4 Special warnings and precautions for use

Hypoglycemia

The risk of hypoglycemia may increase with concomitant use of trelagliptin and sulfonylureas or insulin preparations. Therefore, reduction of the dosage of sulfonylureas or insulin preparations should be considered to reduce the risk of hypoglycemia when used in combination with trelagliptin.

Acute Pancreatitis

Acute pancreatitis has been associated with other DPP-4 inhibitors. After initiation of trelagliptin, patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, trelagliptin should be promptly discontinued and appropriate management should be initiated.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically meaningful interactions (with both drug and food) were observed, and no need for dose adjustment of trelagliptin or other concomitantly administered drugs was identified.

Trelagliptin is primarily renally excreted. Cytochrome (CYP) P450-related metabolism is negligible. No significant drug-drug interactions were observed with the CYP-substrates tested.

Effects of other medicinal products on trelagliptin

Results from clinical interaction studies demonstrate that there are no clinically relevant effects of glimepiride or metformin on the pharmacokinetics of trelagliptin.

Effects of trelagliptin on other medical products

In vitro studies suggest that trelagliptin does not inhibit nor induce CYP 450 isoforms at concentrations achieved with the recommended dose of 100 mg trelagliptin (see section 5.2).

Trelagliptin is a substrate of P-glycoprotein and *in vitro* studies showed slight inhibition of transport of digoxin through P-glycoprotein (IC_{50} value : 500 µmol/L or higher) or showed inhibition of uptake of metformin, an organic cationic transporter-2 (OCT2) substrate (IC_{50} value : 55.9 µmol/L).

In clinical studies, trelagliptin had no clinically relevant effect on the pharmacokinetics of caffeine, tolbutamide, dextromethorphan, midazolam, metformin, or glimepiride, thus providing in vivo evidence of a low propensity to cause interaction with substrates of CYP1A2, CYP2C9, CYP2D6, CYP3A4 or OCT2.

4.6 Pregnancy and lactation

No clinical studies have been conducted to date to evaluate trelagliptin in subjects who are pregnant or lactating. In animal studies, no embryo-fetal toxicity or pre- and postnatal toxicity was observed at dose of up to 300 mg/kg/day in rats and no embryo-fetal toxicity was observed at doses of up to 250 mg/kg/day in rabbits (approximately 31- and 60- fold, respectively, the clinical AUC_{24} (SYR-472/CPH-002)). Placental transfer of trelagliptin was observed in pregnant rats.

It is unknown if trelagliptin is excreted in human milk. In animal study, trelagliptin was secreted in the milk of lactating rats.

As a precaution, trelagliptin should not be administered to women who are or may be pregnant, unless the expected therapeutic benefit is thought to outweigh any possible risk.

During the treatment with trelagliptin, nursing should be avoided if the administration of this drug is necessary for the mother.

4.7 Effects on ability to drive and use machines

The influence of trelagliptin on the ability to drive or use machine is unknown.

4.8 Undesirable Effects

Clinical Trials

Clinical trial data for expected adverse events is based on pooled safety analysis from the following studies: two controlled studies with type 2 diabetes (SYR-472/CCT-001; N= 51 for trelagliptin 50 mg and N= 55 for trelagliptin 100 mg and SYR-472/CCT-002; N=101 for trelagliptin 100 mg) and other two main studies with type 2 diabetes (SYR-472/OCT-001; N=680 for trelagliptin 100 mg and SYR-472/OCT-002; N=14 fortrelagliptin 100 mg). Adverse drug reactions are presented in Table 1.

Table 1. Adverse drug reactions with trelagliptin in clinical studies

	≥ 0.1% to < 5%
Hypersensitivity	Rash Pruritus
Cardiovascular	Atrial fibrillation
Hepatic	ALT increased AST increased γ-GTP increased
Others	Lipase increased Amylase increased

	CPK increased Urinary occult blood positive Nasopharyngitis

4.9 Overdose

There is insufficient information related to overdosage in humans. The highest doses of trelagliptin administered in clinical trials were single doses of 800 mg to healthy subjects.

In thorough QT/QTc study with single administration of trelagliptin 200 mg or 800 mg in healthy subjects, QT prolongation was observed in the trelagliptin 800 mg group. (see section 5.1) Trelagliptin is modestly dialyzable; after 4 hours of hemodialysis, approximately 9.2% of the drug was removed. (see section 5.2)

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Mechanism of Action

By inhibiting dipeptidyl-peptidase-4 (DPP-4) activity which inactivates glucagon-like peptide-1 (GLP-1) secreted into blood from the intestine upon stimulation after oral intake of meals, trelagliptin increases the blood concentration of GLP-1 and promotes insulin secretion by the pancreas dependently on glucose concentration.

Clinical Studies

Phase 2 studies

1. Double-blind comparative study (Dose finding study)/Japan (Study CCT-001)

The results of a double-blind placebo-controlled parallel-design study in which 12.5 mg, 25 mg, 50 mg, 100 mg and 200 mg of trelagliptin was administered for 12 weeks (once a week before breakfast) to patients with type 2 diabetes mellitus with insufficient plasma glucose control despite dietary treatment and/or exercise therapy are shown in Table 2. The means (S.D.) of baseline HbA1c (The National Glycohemoglobin Standardization Program (NGSP value)) were 8.15 (0.95)% , 8.18 (0.89)%, 7.99 (0.77)%, 8.07 (0.86)%, 8.41 (0.97)%, and 7.84 (0.76)% for the placebo, and trelagliptin 12.5
mg, 25 mg, 50 mg, 100 mg, and 200 mg groups, respectively. At the completion of the treatment period, the least squares means (S.E.) of the amount of changes in HbA1c (NGSP value) from baseline were 0.35 (0.068)%, -0.37 (0.068)%, -0.32 (0.070)%, -0.42 (0.070)%, -0.54 (0.068)%, and -0.55 (0.069)% for the placebo, and the trelagliptin 12.5 mg, 25 mg, 50 mg, 100 mg, and 200 mg groups, respectively; a significant decrease in HbA1c was observed in each trelagliptin group compared with the placebo group (pairwise comparisons by contrast test based on the analysis of covariance model using baseline HbA1c (NGSP value) as a covariate: $p < 0.0001$).

Table 2. Changes from baseline in glycemic parameters at End of treatment (Study CCT-001)

Treatment Group	HbA1c † (NGSP value) (%)	Difference vs. Placebo	FPG † (mg/dL)	Difference vs. Placebo	2h PPG † (mg/dL)	Difference vs. Placebo
Trelagliptin 200 mg	-0.54 ± 0.44 (n=54)	-0.89 [-1.10, -0.69]	-12.4 ± 20.2 (n=54)	-22.2 [-30.0, -14.4]	-37.5 ± 33.7 (n=53)	-53.5 [-69.6, -37.4]
Trelagliptin 100 mg	-0.55 ± 0.50 (n=55)	-0.90 [-1.12, -0.69]	-11.5 ± 22.6 (n=55)	-21.4 [-29.5, -13.2]	-32.4 ± 36.6 (n=54)	-48.5 [-64.9, -32.0]
Trelagliptin 50 mg	-0.42 ± 0.46 (n=51)	-0.77 [-0.99, -0.56]	-7.6 ± 33.6 (n=51)	-17.5 [-28.1, -6.8]	-19.1 ± 49.3 (n=51)	-35.1 [-54.2, -16.1]
Trelagliptin 25 mg	-0.32 ± 0.47 (n=51)	-0.67 [-0.88, -0.45]	-10.5 ± 19.7 (n=51)	-20.3 [-28.1, -12.5]	-25.7 ± 37.2 (n=49)	-41.7 [-58.8, -24.6]
Trelagliptin 12.5 mg	-0.37 ± 0.49 (n=54)	-0.72 [-0.94, -0.51]	-5.4 ± 15.1 (n=54)	-15.2 [-22.1, -8.4]	-23.1 ± 30.4 (n=53)	-39.2 [-54.8, -23.6]
Placebo	0.35 ± 0.63 (n=55)		9.8 ± 20.7 (n=55)		16.0 ± 48.6 (n=53)	

† : Mean ± S.D.,

*: [ ] shows two-sided 95% confidence interval

2. Phase 2 dose-ranging study (daily administration)/The United States etc. (Study 006)

The results of a double-blind, randomized, active - and placebo-controlled, parallel-group comparison study in which 3.125 mg, 12.5 mg, 50 mg, and 100 mg of trelagliptin (once daily) and 100 mg of sitagliptin (once daily) were administered for 12 weeks to type 2 diabetic patients with inadequate glycemic control despite lifestyle modification (diet/exercise) or metformin monotherapy are shown in Table 3.

The means (S.D.) of baseline HbA1c (NGSP value) was 8.04 (0.861)%, 8.09 (0.883)%, 8.02 (0.826)%, 8.07 (0.873)%, 8.10 (0.814)%, and 8.00 (0.770)%, for the placebo, trelagliptin 3.125 mg, 12.5 mg, 50 mg, 100 mg, and sitagliptin 100 mg groups, respectively. The LS mean change from Baseline to Week 12 (Last Observation Carried Forward (LOCF)) was -0.04%, -0.65%, -0.61%, -0.77%, -0.59%, and -0.64%, for the placebo, trelagliptin 3.125 mg, 12.5 mg, 50 mg, 100 mg, and sitagliptin 100 mg groups, respectively, showing that HbA1c significantly decreased in all trelagliptin groups and the sitagliptin 100 mg group compared with the placebo group.

Table 3. Changes from baseline in glycemic parameters at Week 12 (LOCF) (Study 006)

Treatment Group	HbA1c (%) †	Difference vs. Placebo	FPG (mg/dL) †	Difference vs. Placebo
Trelagliptin 100 mg	-0.59 ± 0.094 (n=65)	-0.56 * [-0.80, -0.31]	-20.48 ± 4.688 (n=65)	-19.39 [-31.64, -7.13]
Trelagliptin 50 mg	-0.77 ± 0.096 (n=61)	-0.73 * [-0.98, -0.48]	-20.92 ± 4.797 (n=61)	-19.82 [-32.27, -7.37]
Trelagliptin 12.5 mg	-0.61 ± 0.094 (n=63)	-0.57 * [-0.82, -0.33]	-9.40 ± 4.693 (n=63)	-8.30 [-20.66, 4.05]
Trelagliptin 3.125 mg	-0.65 ± 0.095 (n=63)	-0.62 * [-0.86, -0.37]	-18.38 ± 4.779 (n=63)	-17.29 [-29.64, -4.93]
Sitagliptin 100 mg	-0.64 ± 0.096 (n=61)	-0.61 * [-0.85, -0.36]	-16.56 ± 4.822 (n=61)	-15.46 [-27.92, -3.01]
Placebo	-0.04 ± 0.095 (n=63)		-1.10 ± 4.756 (n=62)	

†: Least squares mean ± S.E.

*: p<0.001, [ ] shows two-sided 95% confidence interval

3. Phase 2 dose-ranging study (weekly treatment)/The United States etc. (Study 007)

The results of a double-blind, randomized, placebo-controlled, parallel-group comparison study in which 25 mg, 50 mg, 100 mg, and 200 mg of trelagliptin were administered for 12 weeks to type 2 diabetic patients with inadequate glycemic control despite lifestyle modification (diet/exercise) or metformin monotherapy are shown in Table 4. The means (S.D.) of baseline HbA1c (NGSP value) was 7.91 (0.766)%, 8.05 (0.885)%, 7.91 (0.804)%, 8.04 (0.947)%, and 7.95 (0.776)%, for the placebo, trelagliptin 25 mg, 50 mg, 100 mg, and 200 mg groups, respectively. The LS mean change from Baseline in HbA1c at Week 12 (LOCF) was -0.07%, -0.43%, -0.42%, -0.57%, and -0.57% in the placebo, 25 mg, 50 mg, 100 mg, and 200 mg groups, respectively, showing that HbA1c significantly decreased in all trelagliptin treatment groups compared with the placebo group. Differences in LS mean change from Baseline in HbA1c between all trelagliptin groups and the placebo group showed that HbA1c significantly decreased in all trelagliptin treatment groups at all visits.

Table 4. Changes from baseline in HbA1c at Week 12 (LOCF) (Study 007)

Treatment Group	HbA1c (%) †	Difference vs. Placebo	FPG (mg/dL) †	Difference vs. Placebo
Trelagliptin 200 mg	-0.57 ± 0.076 (n=74)	-0.50 * [-0.70, -0.30]	-10.89 ± 4.392 (n=74)	-14.35 [-25.68, -3.02]
Trelagliptin 100 mg	-0.57 ± 0.077 (n=72)	-0.50 * [-0.70, -0.30]	-10.97 ± 4.400 (n=72)	-14.43 [-25.81, -3.05]
Trelagliptin 50 mg	-0.42 ± 0.078 (n=71)	-0.35 * [-0.55, -0.15]	-1.90 ± 4.483 (n=71)	-5.36 [-16.78, 6.06]
Trelagliptin 25 mg	-0.43 ± 0.078 (n=70)	-0.36 * [-0.56, -0.16]	-9.63 ± 4.466 (n=70)	-13.09 [-24.55, -1.62]
Placebo	-0.07 ± 0.077 (n=71)		3.46 ± 4.424 (n=71)	

†: Least squares mean ± S.E.

*: p<0.001, [ ] shows two-sided 95% confidence interval

Phase 3 Studies

1. Double-blind comparative study (Confirmatory study)/Japan (Study CCT-002)

The results of a double-blind alogliptin-controlled parallel-design study in which 100 mg of trelagliptin (once a week before breakfast) and 25 mg of alogliptin (once daily before breakfast) were administered for 24 weeks to patients with type 2 diabetes mellitus with insufficient plasma glucose control despite dietary treatment and/or exercise therapy are shown in Table 5. The means (S.D.) of baseline HbA1c were 7.73 (0.85)% in the trelagliptin 100 mg group and 7.87 (0.86)% in the alogliptin 25 mg group. At the completion of the treatment period, difference between the groups in the least squares mean of the amount of changes in HbA1c (NGSP value) from baseline confirmed non-inferiority (acceptable margin: 0.40%) of treatment with trelagliptin 100 mg to treatment with alogliptin 25 mg.

Table 5. Changes from baseline in glycemic parameters at End of treatment (Study CCT-002)

Treatment Group	HbA1c (NGSP value) * (%)	Difference vs. alogliptin	FPG ** (mg/dL)	Differencevs alogliptin	2h PPG ** (mg/dL)	Difference vs. alogliptin
Trelagliptin 100 mg	-0.33 ± 0.06 (n=101)	0.11 [-0.05, 0.28]	-6.4 ± 21.2 (n=101)	8.6 [1.7, 15.5]	-17.2 ± 47.7 (n=97)	12.1 [-0.9, 25.1]
Alogliptin 25mg	-0.45 ± 0.06 (n=92)		-14.9 ± 27.0 (n=92)		-29.2 ± 42.2 (n=90)	

*: Least squares mean ± S.E. adjusted by baseline HbA1c (NGSP value), [ ] shows two-sided 95% confidence interval

**: Mean ± S.D., [ ] shows two-sided 95% confidence interval

2. Long-term administration study/Japan (Study OCT-001)

The results of a study in which 100 mg of trelagliptin (once a week before breakfast) was administered for 52 weeks to patients with type 2 diabetes mellitus with insufficient plasma glucose control despite dietary treatment and/or exercise therapy, or administration of oral hypoglycemic drugs in addition to dietary treatment and/or exercise therapy are shown in Table 6.

Table 6. Changes from baseline in HbA1c at End of treatment (Study OCT-001)

	HbA1c (NGSP value) (%)	
	Baseline value	**Change from baseline**
Trelagliptin alone	7.87 ± 0.87 (n = 248)	-0.57 ± 0.88 (n = 248)
Sulfonylureas combination	8.09 ± 0.84 (n = 158)	-0.37 ± 0.90 (n = 158)
Fast acting insulin secretagogues combination	7.87 ± 0.78 (n = 67)	-0.25 ± 0.78 (n = 66)
α-glucosidase inhibitors combination	8.07 ± 0.98 (n = 65)	-0.67 ± 0.74 (n = 65)
Biguanides combination	7.82 ± 0.94 (n = 70)	-0.31 ± 0.82 (n = 70)
Thiazolidinediones combination	7.91 ± 0.96 (n = 72)	-0.74 ± 0.65 (n = 72)

Mean ± S.D.

3. Study of drug switching from other DPP-4 inhibitors (once daily administration)/Japan (OCT-002)

The results of a study of drug switching in which 100 mg of trelagliptin (once a week before breakfast) was administered for 12 weeks to 14 patients with type 2 diabetes mellitus who had received conventional DPP-4 inhibitors once daily in addition to dietary treatment and/or exercise therapy are shown in Table 7.

Table 7. Changes from switching in glycemic parameters at End of treatment (Study OCT-002)

	HbA1c (NGSP value) (%)	**FPG (mg/dL)**	**2h PPG (mg/dL)**
Value before switching	7.06 ± 0.49 (n = 14)	140.5 ± 23.3 (n = 14)	202.1 ± 38.3 (n = 14)
Change from switching	0.04 ± 0.36 (n = 14)	-1.6 ± 13.9 (n = 14)	-8.7 ± 25.4 * (n = 14)

Mean ± S.D.

*: 7 days after switching to trelagliptin

Pharmacoligical study to evaluate the effect on QT/QTc interval prolongation

1. QT/QTc study/Australia (CPH-005)

When 200 mg and 800 mg of trelagliptin in a single dose were orally administered to 66 and 65 healthy adults, respectively, the maximum difference from the placebo group in the amount of change from time-matched baseline QTcF interval (the upper limit of two-sided 90% confidence interval) was 3.5 (5.85) msec at 6 hours after administration in the 200 mg dose group, while it was 11.0 (13.77) msec at 2 hours after administration in the 800 mg dose group (the upper limit of the confidence interval exceeded 10 msec at 1.5 to 8 hours after administration in the 800 mg dose group).

5.2 Pharmacokinetic Properties

Absorption

1. Single dose

When trelagliptin (50 mg and 100mg) was administered to 8 healthy adults in a single dose 30minutes before breakfast, the pharmacokinetic parameters of trelagliptin were presented in below table.

Dosage	N	C_{max} (ng/mL)	T_{max} (h)	AUC_{∞} (ng · h/mL)	$t_{1/2z}$ (h)	C_{168} (ng/mL)
50 mg	8	268.3 (88.8)	1.3 (1.0, 3.0)	3106.7 (329.3)	53.9 (6.6)	1.2 (0.5)
100 mg	8	619.4 (77.3)	1.3 (1.0, 2.0)	6601.7 (845.4)	54.3 (7.9)	2.1 (0.7)

mean (S.D.), T_{max} is expressed by median (minimum, maximum)

2. Multiple dose

When 100 mg of trelagliptin was administered to 9 healthy adults in a single dose 30 minutes before breakfast (on day 1) and once daily 30 minutes before breakfast for 11 days (from day 4 to 14), the mean (S.D.) C_{max} and AUC_{∞} on day 1 were 544.3(122.0) ng/mL and 5572.3(793.2)ng·h/mL, respectively, and the mean (S.D.) C_{max} and AUC_T on day 14 were 602.6(149.5)ng/mL and 5292.9(613.8) ng·h/mL, respectively.

3. Effect of food

When 100 mg of trelagliptin was administered to 12 healthy adults 30 minutes after the start of breakfast, the C_{max} increased by 16.8% and AUC_{∞} decreased by 2.5% compared with those after administration under fasting conditions.

Distribution

When [^{14}C] trelagliptin was added to human plasma at the concentration of 0.01-10 μg/mL, the protein binding ratio was 22.1% - 27.6% (*in vitro*).

The percent distribution of trelagliptin at the concentration of 0.1-10 µg/mL in blood cells was 49.2% - 55.0% (in vitro).

Metabolism

Trelagliptin is metabolized into an active metabolite M-I via N-demethylation mainly by CYP2D6. Human plasma concentrations of an active metabolite M-I were less than 1% of trelagliptin.

Trelagliptin showed a weak inhibitory effect on CYP3A4/5 (direct inhibition, IC_{50} value of 100 µmol/L or higher; metabolism-based inhibition, IC_{50} values of 12 µmol/L (midazolam 1'-hydroxylation activity) and 28 µmol/L (testosterone 6ß-hydroxylation activity), but did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6, and did not induce CYP1A2, CYP2B6, or CYP3A4 (*in vitro*).

Excretion and Elimination

When trelagliptin (50 mg and 100 mg) was administered to 8 healthy adults in a single dose 30 minutes before breakfast, the cumulative urinary excretion rate of trelagliptin up to 168 hours after administration was 71.45% and 75.96%, respectively. The renal clearance of trelagliptin was 11.6 L/h.

Trelagliptin is a P-glycoprotein substrate.

Trelagliptin inhibited P-glycoprotein (IC_{50} value: 500 µmol/L or higher) and OCT2 (IC_{50} value: 55.9 µmol/L), but did not inhibit BCRP, OATP1B1, OATP1B3, OAT1 or OAT3 (*in vitro*).

Special Populations

Impaired Renal Function

When 50 mg of trelagliptin was administered to patients with renal impairment and healthy adults in a single dose, AUC_{last} and C_{max} increased by 55.7% and 36.3% in 6 patients with mild renal impairment (Ccr = 50-80 mL/min), increased by 105.7% and 12.9% in 6 patients with moderate renal impairment (Ccr = 30-50 mL/min), increased by 201.4% and 9.1% in 6 patients with severe renal impairment (Ccr < 30 mL/min), and increased by 268.1% and decreased by 13.8% in 6 patients with end-stage renal disease as compared with those of age-, sex-, race-, and weight-matched healthy adults. In addition, 9.2% of the dose of trelagliptin was removed from the body during a 4-hour dialysis procedure.

Impaired Hepatic Function

When 50 mg of trelagliptin was administered to 8 patients with moderate hepatic impairment (Child-Pugh score of 7-9) and 8 healthy adults in a single dose, AUC_{∞} and C_{max} in patients with moderate hepatic impairment increased by 5.1% and decreased by 4.3%, respectively, compared with those of age-, sex-, race-, smoking history-, and weight-matched healthy adults.

Age, Gender, Race

Age and gender did not have any clinically relevant effect on the pharmacokinetcs of trelagliptin. The pharmacokinetics of trelagliptin has not been evaluated in children.

There were no major differences in AUC_{∞} or C_{max} of trelagliptin between Japanese and Caucasian.

Drug Interactions

Glimepiride

When 200 mg of trelagliptin was repeatedly administered to 12 healthy adults once daily for 11 days and was coadministered with 1 mg of glimepiride in a single dose on day 11 of trelagliptin administration, the point estimates [two-sided 90% confidence interval] of the least squares mean ratios of AUC_{∞} and C_{max} of glimepiride coadministered with trelagliptin were 103.5% [99.1, 108.1] and 121.5% [109.6, 134.8], respectively, compared with glimepiride alone.

Metformin

When 100 mg of trelagliptin once daily and 1000 mg of metformin twice daily were repeatedly administered for 12 days to 48 healthy adults (crossover study), the point estimates [two-sided 90% confidence interval] of the least squares mean ratios of AUC_T and C_{max} of trelagliptin coadministered with metformin were 105.0% [102.3, 107.8] and 108.5% [100.6, 117.0] compared with trelagliptin alone. The point estimates [two-sided 90% confidence interval] of the least squares mean ratios of AUC_T and C_{max} of metformin coadministered with trelagliptin were 90.4% [84.1, 97.2] and 73.3% [66.6, 80.6], compared with metformin alone.

Caffeine, Tolbutamide, Dextromethorphan, Midazolam

When 100 mg of trelagliptin was repeatedly administered once daily for 11 days to 18 healthy adults and was coadministered with drug cocktail (200 mg of caffeine, 500 mg of tolbutamide, 30 mg of dextromethorphan, and 4 mg of midazolam) in a single dose on day 11, the two-sided 90% confidence intervals of the least squares mean ratios of caffeine, tolbutamide, midazolam, and respective metabolites coadministered with trelagliptin were within the range between 80% and 125% compared with drug cocktail alone. The point estimates [two-sided 90% confidence interval] of the least squares mean ratios of AUC_{last} and C_{max} of dextromethorphan coadministered with trelagliptin were 117.9% [98.8, 140.7] and 111.3% [95.5, 129.8], while the two-sided 90% confidence intervals of the least squares mean ratios of AUC_{last} and C_{max} of a metabolite dextrophan were within the range between 80% and 125%.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Trelagliptin was not carcinogenic in the 2-year carcinogenicity studies in rats and mice.

In the 2-year carcinogenicity studies, mice and rats were administered oral doses of 100, 300 or 1000 mg/kg/day and 25/50, 75/150, 250/500, or 750/1500 mg/kg/day in male/female rats, respectively. The maximum doses used in the mouse and rat studies (1000 mg/kg/day in mice, 750 mg/kg/day in male rats and 1500 mg/kg/day in female rats) provided exposure margins that were approximately 126-, 116- and 201-fold, respectively, higher than the clinical AUC_{24} which was obtained after repeated administration of trelagliptin at

100 mg/day for 11 days starting from 3 days after a single dose to healthy adult men in the Japanese phase I repeat-dose study (SYR-472/CPH-002).

Trelagliptin was not mutagenic or clastogenic, with and without metabolic activation, in the Ames test with S. typhimurium and E. coli or the cytogenetic assay in mouse lymphoma cells.

Trelagliptin was negative in the in vivo mouse micronucleus study.

In a fertility study in rats, no adverse effects on early embryonic development, mating, or male/female fertility was observed at doses up to 1000 mg/kg, or approximately 111-fold higher than the clinical AUC_{24} (SYR-472/CPH-002).

Animal Toxicology and/or Pharmacology

NOAELs (No Observed Adverse Effect Levels) in repeated dose toxicity studies with longest treatment period were 250 mg/kg/day in the 26-week toxicity study in rats and 100 mg/kg/day in the 39-week toxicity study in dogs. These NOAELs in rats and dogs provided exposure multiples of approximately 41- and 59-fold, respectively, higher than the clinical AUC_{24} (SYR-472/CPH-002).

Administration of trelagliptin did not result in any drug-related skin lesions in monkeys, a finding that has been observed in studies conducted with some other DPP-4 inhibitors. No phototoxicity was noted in hairless mice.

6. Pharmaceutical Particulars

6.1 List of excipients

Tablet core: D-Mannitol, Microcrystalline cellulose, Croscarmellose sodium, Hydroxypropylcellulose and Sodium stearyl fumarate.

Tablet film coat: Hypromellose, Macrogol 6000*, Titanium oxide, Yellow ferric oxide (50mg only), Red ferric oxide and Printing ink (Gray F1).

* Macrogol 6000 is a name in the Japanese Pharmacopoeia. Its average molecular mass is approximately 8300. Therefore it is different from Macrogol 6000 in European Pharmacopoeia (Ph.Eur.) or Polyethylene Glycol 6000 in US National Formulary (NF) whose average molecular mass is 6000 and it is equivalent to Macrogol 8000 in Ph. Eur. and Polyethylene Glycol 8000 in NF.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years (see on outer carton)

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

Blister (Polyvinylchloride (PVC) film/Aluminum foil) in blister card

Box of 20 tablets (20 blister cards)

7. Marketing Authorization Holder

Manufactured by: Takeda Pharmaceutical Company Limited, Osaka Plant, Osaka, Japan

Primary and secondary packed and final released by: Kanae Co., Ltd., Tochigi, Japan

Imported by: Takeda (Thailand), Ltd., Bangkok

8. Marketing Authorization Number

1C XX/XX (NC)

9. Date of authorization

xx xxx xxxx

10. Date of revision of the text

October 2017