**Only for the use of Medical Professionals/Endocrinologist*

WEDICA

Trelagliptin

COMPOSITION

Wedica 50 Tablet : Each film coated tablet contains Trelagliptin Succinate INN equivalent to Trelagliptin 50 mg.

Wedica 100 Tablet : Each film coated tablet contains Trelagliptin Succinate INN equivalent to Trelagliptin 100 mg.

Therapeutic Class: Anti-Diabetic Drug.

PHARMACOLOGICAL ACTION

Mechanism of Action

By inhibiting the activity of dipeptidyl peptidase 4 Trelagliptin inactivates glucagon-like peptide 1 (GLP-1) from secretion from the intestines to the blood via stimulation from oral intake of food, increases GLP-1 blood concentration and promotes blood glucose concentration-dependent insulin secretion from the pancreas.

1. DPP- 4 Inhibition

a) Selectively inhibits human plasma DPP-4 activity (IC50 value: 4.2 nmol/L) *(in vitro)*. Moreover, when IC50 value (nmol/L) was compared under similar conditions *(in vitro)* in order to compare Trelagliptin and alogliptin DPP-4 inhibitory action, values were 1.3 and 5.3 respectively.

b) Type 2 diabetes patients who exhibit insufficient blood glucose control through dietary and exercise measures were given 100 mg of Trelagliptin (once weekly, before meal) for 12 weeks. The results of the double blind, parallel group, placebo-controlled comparative study show that 7 daysafter final treatment, the average DPP-4 inhibition rate was 77.4% compared in the Trelagliptin 100 mg group.

2. Active Type GLP-1 Concentration Elevation

Type 2 diabetes patients who exhibit insufficient blood glucose control through dietary and exercise measures were given 100mg of Trelagliptin orally (once weekly, before meal) for 12 weeks. The results of the double-blind, parallel group, placebo-controlled comparative study showed GLP-1 concentrations with meal load tests conducted 12 weeks after administration to be significantly elevated relative to the placebo group.

3. Glucose Tolerance Improvement

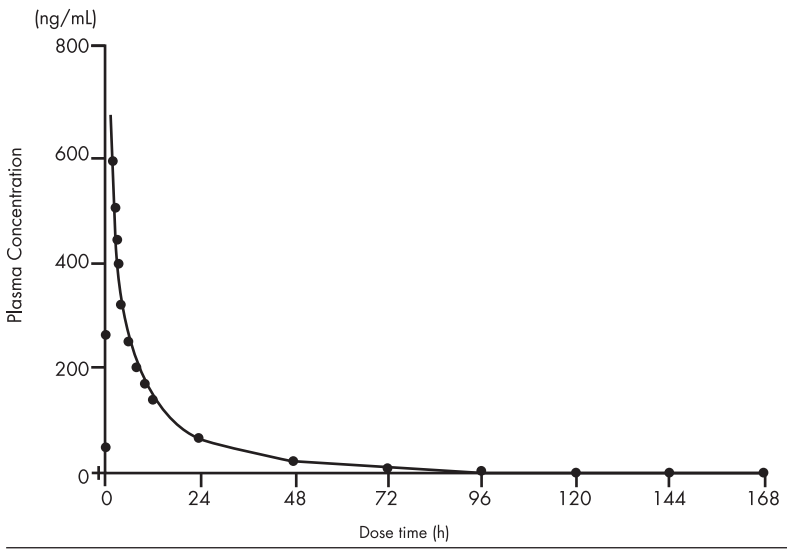
A single, oral dose of Trelagliptin was given to obese type 2 diabetic model organisms (Wister fatty rat) and non-obese type 2 diabetic model organisms (N-STZ-1.5 rat) after 1 night of fasting. Glucose was then given orally 1 hour after drug administration to conduct a glucose load test. Results from the tests revealed a glucose tolerance-improving action.

PHARMACOKINATICS

1. Blood concentration

a) Single Dose

Healthy adults (8) were given Trelagliptin 100mg 30 minutes before meal, resulting in the following single does blood serum concentration and pharmacological parameters. 168 hours after administration, serum blood concentration was an average of 2.1ng/mL.



Dosage	C_{max} ng/mL	T_{max} (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$T_{1/2}$ (0-72) (h)	$T_{1/2}$ (0-168) (h)
100mg	619.4 (77.3)	1.3 (0.4)	6,601.7 (845.4)	18.5 (1.9)	54.3 (7.9)

Average value (standard deviation)

b) Repeated Dose

Healthy adults (9) were given Trelagliptin at 100mg 30 minutes before meal once daily. After 3 days, once daily repeat dosages were given 30 minutes before meal for 11 days. Day-1 C_{max} and $AUC_{(0\text{-}Inf)}$ were 544.3 (122.0) ng/mL and 5,572.3 (793.2) ng·h/mL respectively. Day-14 C_{max} and $AUC_{(0\text{-}tau)}$ average values (standard deviation) were 602.6 (149.5) ng/mL and 5,292.9 (613.8) ng·h/mL respectively.

(Approved administration and dosage for this drug consists of normally, 100 mg of Trelagliptin is administered to adults once weekly by mouth.

c) Dietary effects

Healthy adults (12) were given Trelagliptin at 100mg 30 minutes before meal, resulting in a C_{max} and $AUC_{(0\text{-}inf)}$ 16.8% and 2.5% greater compared to fasting administration, respectively.

2. Plasma Protein Binding Rate

Trelagliptin at a concentration of 0.1～10μg/mL was added to human plasma, resulting in a plasma protein binding rate of 22.1～27.6% *(in vitro)*.

3. Metabolism

a) Trelagliptin is metabolized mainly by CYP2D6 N -demethylation from the active metabolite M-1.Moreover, human plasma metabolite M-1 consisted of less than 1% unaltered Trelagliptin.

b) Trelagliptin demonstrates weak inhibition of CYP3A4/5.

However, (direct inhibitory action IC50 value: 100μmol/L or more, metabolic inhibitory action IC50 value: 12μmol/(L midazolam 1'-hydroxylation activity) and 28μmol/(L testosterone 6β-hydroxylation activity)), C Y P1A2, C Y P2B6、, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 were not inhibited, and

CYP1A2, CYP2B6, and CYP3A4 were not induced *(in vitro)*.

4. Elimination

a) Healthy adults (12) were given a single dose of Trelagliptin 100mg in a fasted state or 30 minutes after the start of meal. Trelagliptin accumulation in the urine AUC were 76.6% and 76.1% respectively 168 hours after administration.

b) Trelagliptin is a P-glycoprotein substrate and sightly inhibits digoxin infusion via P-glycoprotein action (IC50：500μmol/L or more). Moreover, Trelagliptin demonstrates inhibitory action on organiccation transporter OCT2 involved with metformin processing (IC50 value: 55.9μmol/L) *(in vitro)*.

5. Action with Kidney Disease

Individuals with kidney disease and healthy adults were given a single dose of Trelagliptin at 50mg, resulting in the following AUC (0-tlqc) and Cmaxvalues. When compared to healthy adults with respect to age, gender, ethnicity, and body weight, individuals with kidney disease (Ccr=50～80mL/min、6 cases) showed a 55.7% increase, 36.3% increase, patients with moderate kidney function disorder (Ccr=30～50mL/min、6 cases) showed 105.7% increase, 12.9% increase, patients with severe kidney function disorder (Ccr<30mL/min、6 cases) showed 201.4% increase, 9.1% increase, end stage kidney disease patients (6 cases) showed 268.1% increase, 13.8% reduction. Moreover, 9.2% of the Trelagliptin dosage was removed after 4 hours of dialysis.

Approved administration and dosage for this drug consists ofnormally, 100mg of Trelagliptin is administered to adults once weekly by mouth.

6. Activity with Liver Disease

Individuals with moderate liver disease (Child-Pugh score of 7~9, 8 cases) and healthy adults (8 were given a single dose of Trelagliptin at 50 mg, resulting in the following $AUC_{(0\text{-}inf)}$ and C_{max} values. When compared to healthy adults with respect to age, gender, ethnicity, smoking, and body weight, $AUC_{(0\text{-}inf)}$ increased 5.1% and C_{max} increased 4.3%.

INDICATION

Indicated for type 2 diabetes mellitus. When the first line treatment of metformin is not achieving the expected glycemic goals.

DOSAGE & ADMINISTRATION

100 mg of Trelagliptin is administered to adults once weekly by mouth.

Cautions Related to Methods and Dose

1) For patients with moderate kidney function disease, given that blood drug concentration will elevate due to delayed elimination, reduce dosage with reference to the chart below.

Dosage for patients with moderate kidney function disease

	Serum creatinine (mg/dL) *	Creatinine Clearance (Ccr, mL/min)	Dose
Patients with moderate	Males: 1.4<～ 2.4 Females: 1.2<～2.0	30 ～<50	50mg weekly

* Calculated value equivalent to Cc (60 years old, 65kg)

2) Instruct the patient regarding the following points:

a) This medication is to be takenonce weekly,and on the same day every week.

b) If patient forgets to take medication as scheduled, only take the quantityintended for the time in which the forgotten dose was realized, and then continue dosage according to a newly decided schedule afterwards.

WARNINGS

(provide cautious dosage to the following patients): The following patients or circumstances

1) Patients with moderate kidney function disorder

2) Patients undergoing treatment with sulfonylurea drugs or insulin medication [there are reports of severe hypotension with use in combination with other DPP-4 inhibitors]

3) Hypopituitarism or hypoadrenalism

4) Malnutrition, starvation, irregular eating patterns, insufficient eating, or hyposthenia

5) Vigorous exercise

6) Patients who consume excessive alcohol

Major Warnings

1) This drug may cause hypoglycemia when used in combination with other diabetes medications, so thoroughly explain and caution the patient of such risks of hyoglycemia when combining with other medications. There is an increased risk of hypoglycemia particularly when combined with sulfonylurea drugs and insulin medications. Consider reducing the dose of sulfonylurea drugs or insulin medication when used in combination with these drugs in order to lessen the risk of hypoglycemia.

2) This drug is to be taken orally once per week. Effects may persist even after dosage is ceased, so take sufficient notice of blood sugar values and side effects. Moreover, evaluate the starting period and dose based on the state of blood sugar management when using other diabetes medications after cessation of this medication.

3) Only consider application for patients with established diagnosis of diabetes mellitus. Pay attention to conditions that show abnormal sugar resistance, glucosurea, and other symptoms resembling diabetes (renal glucosuriea, thyroid function abnormality, etc.)

4) Application of this drug should only be considered once diet- and exercise-based diabetes treatments have already been implemented with unsatisfactory results.

5) During administration of this drug, progress should be sufficiently observed along with quantitative blood sugar measurements. If no results are seen after 2 to 3 months of treatment, consider changing to a more appropriate treatment method.

6) During dosage maintenance, the medication may no longer become necessary, or the effects of the drug may diminish due to complications with poor nutrition or infectious disease. In such cases, evaluate continuation of normal does, medication selection, etc. upon consideration of dietary volume, blood sugar levels, and presence of infectious symptoms.

7) Warn patients that work in high places, operate machinery, etc., as low blood sugar can occur.

8) Clinical results and safety regarding combination with insulin medication has not been investigated.

9) This drug and GLP-1 receptor agonists both possess the ability to lower blood sugar and assist GLP-1 receptor agonists.There are no clinical study results regarding the combination of these medications, and neither the efficacy nor the safety can be confirmed.

DRUG INTERACTIONS

This drug is mainly eliminated by the kidneys in an unaltered form. Excretion has been observed to take place via the urine following the usual glomerular route (warning of possible side effects)

Drug name, etc.	Clinical symptoms, safeguards, mode of
Diabetes medication Sulfonylurea Drugs Glimepiride, Glibenclamide, Gliclazide, Tolbutamide, etc. Rapid Insulin Secretagogue Nateglinide, Mitiglinide Calcium Hydrate, Nateglinide -Glucosidase Inhibitor Voglibose, Acarbose, Miglitol Biguanide Class Drugs Metformin Hydrochloride, Buformin Hydrochloride Thiazolidine Class Drugs Pioglitazone Hydrochloride Glp-1 Receptor Agonist Liraglutide, Exenatide, Lixisenatide Sglt2 Inhibitors Ipragliflozin L-proline , Dapagliflozin Propylene Luseogliflozin Hydrate, Glycolate Hydrate, Luseogliflozin Hydrate, Etc. Insulin Medications	when used in combination with diabetes medications indicated on the left Can cause low blood sugar present, so administer using cautious dosage Particularly with sulfonylurea drugs or insulin medications Risk of low blood sugar when used Risk of increased hypoglycemia from these medications In order to alleviate this, consider sulfonylurea drugs or insulin medications reduction. α-Glucosidase inhibitor with Confirm decreased blood sugar. combined use with In such cases, administer sucrose or fructose.
Drugs that, in combination, enhance or diminish the blood sugar-lowering effect If using other drugs in combination, Enhances the blood sugar-lowering effect of diambeetdeiscamtieodnications β-blockers, Salicylic acid medications, Monoamine oxidase inhibitors, Fibrate-type hyperlipidemia medications, etc. Diminishes the blood sugar-lowering effect of diambeetdeiscamtieodnications Adrenaline, Adrenocortical hormone, Parathyroid hormone, etc	are listed to the left. insulinsecretagogues to this drug Sufficient influence when added Exercise caution

SIDE EFFECTS

Among 901 domestic clinical trial cases up to the time of approval, 103 cases (11.4%) showed clinical results that included abnormalities and side effects. These mainly included hypoglycemia, nasopharyngitis, and elevated lipase.

1) Given the appearance of serious side effects such as hypoglycemia (0.1～5%), administer medication in conjunction with close observation of patient status. Other DPP-4 inhibitors have been reported to present serious hypoglycemia in combination with Sulfonylurea medications as well as some cases of loss of consciousness. Moreover, decreased blood sugar from the use of this medication, once confirmed, can be remedied by giving sucrose. However, hypoglycemia resulting from a combination with-glucosidaseinhibitors should be treated with fructose.

Major side effects (drug type)

1) Acute pancreatitis can occur, so careful observation is called for and sustained, intense abdominal pain, vomiting, and other abnormal symptoms should be followed up with cessation of the drug followed by appropriate measures.

2) Intestinal Obstructions can occur, so conduct careful observation. If severe constipation, abdominal swelling, sustained abdominal pain, vomiting, or other symptoms are observed, stop treatment and take appropriate measures.

3) Other Side Effects: Take appropriate actions depending on the situation if the following side effects arise.

	Between 0.1 and 5%
1) Hypersensitivity	Rash, itch
2) Circulatory system	Atrial fibrillation
3) Liver	Elevated ALT (GPT), AST (GOT), and γ-GTP
4) Other	Elevated serum amylase, lipase, CK (CPK), presence of blood in urine, or nasopharyngitis

4) Administration to Elderly Patients: Since many geriatric patients generally have lowered kidney function, take note of side effects and administer a cautious dose while sufficiently observing treatment progress.

5. Administration to pregnant women, lactating women, or for gynecological use

a) For women who are pregnant or may be pregnant, only administer drug upon fully evaluating the risks and benefits of treatment. The safety of use during pregnancy is not established. There are reports of the drug crossing the placenta in animal (rat) tests.

b) Avoid giving drug to women who are breastfeeding, and stop breastfeeding if drug must be administered.

6. Administration to children: The safety of this drug in infants with low birth weight, newborn infants, nursing infants, babies, and children under the age of 13 is not established

7. Overdose safety information regarding overdose has not been sufficiently collected, for dietary and exercise treatments, as well as metformin-only treatments, or for type 2 diabetes patients in which blood sugar control is not ideal. However, there have been overseas studies in which 100mg of this drug was taken orally every day over 12 consecutive weeks and side effects did not differ from the placebo group. 1

8. Other warnings overseas clinical studies involving single Trelagliptin doses of 800mg reported QT elongation.

PHARMACEUTICAL INFORMATION

Storage conditions

Store at 25^0C; excursions permitted to 15^0 -30^0C. Dispense medication in the original container to protect from exposure to high humidity and light. Keep out of the reach of children.

Presentation & Packaging

Wedica 50 Tablet : Each commercial box contains 2x10s tablets in Alu-Alu blister pack.

Wedica 100 Tablet : Each commercial box contains 2x8s tablets in Alu-Alu blister pack.

Manufactured By
BEACON
Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

For more info:

Only for Export

LF 00000