Wedica 100 Tablet

Generic Name: Trelagliptin Succinate INN equivalent to Trelagliptin 100 mg

Summary of Product Characteristics

1. Name of the Drug Product

Wedica 100 Tablet

2. Qualitative and Quantitative Composition

Formulation per tablet (Each tablet contains Trelagliptin Succinate INN equivalent to Trelagliptin 100 mg)

3. Pharmaceutical Form

Tablet

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of 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 kidney function disease	Males: 1.4<~2.4; Females: 1.2<~2.0	30 ~<50	50 mg weekly

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

2) Instruct the patient regarding the following points: a) This medication is to be taken once weekly, and on the same day every week. b) If patient forgets to take medication as scheduled, only take the quantity intended for the time in which the forgotten dose was realized, and then continue dosage according to a newly decided schedule afterwards.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

(Provide cautious dosage to the following patients):

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; thoroughly explain and caution the patient of such risks when combining with other medications, particularly 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. 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 glucosuria, 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, 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; evaluate continuation of normal dose, 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; there are no clinical study results regarding the combination of these medications, and neither the efficacy nor the safety can be confirmed.

4.5 Interaction with other medicinal products and other forms of interaction

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 action
Diabetes medication: Sulfonylurea Drugs (Glimepiride, Glibenclamide, Gliclazide, Tolbutamide, etc.); Rapid Insulin Secretagogue (Nateglinide, Mitiglinide Calcium Hydrate); α-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, etc.); Insulin Medications	Can cause low blood sugar when used in combination with diabetes medications indicated on the left, so administer using cautious dosage. Particularly with sulfonylurea drugs or insulin medications there is an increased risk of hypoglycemia; consider reducing sulfonylurea drug or insulin medication dose. In case of decreased blood sugar confirmed with an α-glucosidase inhibitor combination, administer sucrose or fructose.
Drugs that enhance the blood sugar-lowering effect: β blockers, Salicylic acid medications, Monoamine oxidase inhibitors, Fibrate-type hyperlipidemia medications, etc.	Sufficient influence when added; exercise caution.
Drugs that diminish the blood sugar-lowering effect: Adrenaline, Adrenocortical hormone, Parathyroid hormone, etc.	When used in combination with these medications, sufficient influence when added; exercise caution.

4.6 Fertility, pregnancy and lactation

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.

4.7 Effects on ability to drive and use machines

Trelagliptin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable 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, including some cases of loss of consciousness. Decreased blood sugar from use of this medication, once confirmed, can be remedied by giving sucrose; hypoglycemia resulting from a combination with α-glucosidase inhibitors should be treated with fructose.

Major side effects (drug type)

1) Acute pancreatitis can occur, so careful observation is called for; 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%
Hypersensitivity	Rash, itch
Circulatory system	Atrial fibrillation
Liver	Elevated ALT (GPT), AST (GOT), and γ-GTP
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose safety information 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 100 mg of this drug was taken orally every day over 12 consecutive weeks and side effects did not differ from the placebo group.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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). When compared under similar conditions (in vitro), Trelagliptin and alogliptin DPP-4 inhibitory action IC50 values were 1.3 and 5.3 nmol/L respectively. b) Type 2 diabetes patients with insufficient blood glucose control through dietary and exercise measures were given 100 mg of Trelagliptin (once weekly, before meal) for 12 weeks. The double blind, parallel group, placebo-controlled comparative study showed that 7 days after final treatment, the average DPP-4 inhibition rate was 77.4% in the Trelagliptin 100 mg group.

2. *Active Type GLP-1 Concentration Elevation*: 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 and non-obese type 2 diabetic model organisms after 1 night

of fasting, followed by an oral glucose load test 1 hour after drug administration. Results revealed a glucose tolerance-improving action.

5.2 Pharmacokinetic properties

1. *Blood concentration*

a) *Single Dose*: Healthy adults (8) were given Trelagliptin 100 mg 30 minutes before meal. 168 hours after administration, serum blood concentration was an average of 2.1 ng/mL. Cmax was 619.4 (77.3) ng/mL, Tmax 1.3 (0.4) h, AUC(0-inf) 6,601.7 (845.4) ng·h/mL, T1/2 (0-72) 18.5 (1.9) h, T1/2 (0-168) 54.3 (7.9) h (average value, standard deviation).

b) *Repeated Dose*: Healthy adults (9) were given Trelagliptin at 100 mg 30 minutes before meal once daily; after 3 days, once daily repeat dosages were given for 11 days. Day-1 Cmax and AUC(0-Inf) were 544.3 (122.0) ng/mL and 5,572.3 (793.2) ng·h/mL respectively; Day-14 Cmax and AUC(0-tau) average values were 602.6 (149.5) ng/mL and 5,292.9 (613.8) ng·h/mL respectively. (Approved dosage is normally 100 mg of Trelagliptin administered to adults once weekly by mouth.)

c) *Dietary effects*: Healthy adults (12) given Trelagliptin at 100 mg 30 minutes before meal showed a Cmax and AUC(0-inf) 16.8% and 2.5% greater compared to fasting administration, respectively.

2. *Plasma Protein Binding Rate*: Trelagliptin at a concentration of 0.1–10 μg/mL added to human plasma resulted 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; human plasma metabolite M-1 consisted of less than 1% unaltered Trelagliptin. b) Trelagliptin demonstrates weak inhibition of CYP3A4/5; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 were not inhibited, and CYP1A2, CYP2B6, and CYP3A4 were not induced (in vitro).

4. *Elimination*: a) Healthy adults (12) given a single dose of Trelagliptin 100 mg in a fasted state or 30 minutes after start of meal showed Trelagliptin accumulation in the urine AUC of 76.6% and 76.1% respectively 168 hours after administration. b) Trelagliptin is a P-glycoprotein substrate and slightly inhibits digoxin infusion via P-glycoprotein action (IC50: 500 μmol/L or more); it also demonstrates inhibitory action on organic cation transporter OCT2 involved with metformin processing (IC50 value: 55.9 μmol/L, in vitro).

5.3 Preclinical safety data

Action with Kidney Disease: Individuals with kidney disease and healthy adults were given a single dose of Trelagliptin at 50 mg. Compared to healthy adults,

individuals with kidney disease (Ccr=50–80 mL/min, 6 cases) showed a 55.7%/36.3% increase in AUC/Cmax; moderate kidney function disorder (Ccr=30–50 mL/min, 6 cases) showed 105.7%/12.9% increase; severe kidney function disorder (Ccr<30 mL/min, 6 cases) showed 201.4%/9.1% increase; end stage kidney disease patients (6 cases) showed 268.1% increase/13.8% reduction. 9.2% of the Trelagliptin dosage was removed after 4 hours of dialysis. Approved dosage is normally 100 mg once weekly by mouth.

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; AUC(0-inf) increased 5.1% and Cmax increased 4.3% compared to healthy adults.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet contents: Pregelatinised Starch (Starch 1500), Sodium Starch Glycolate, Sodium Stearyl Fumarate, Colloidal Anhydrous Silica (Aerosil 200), Purified Talc, Ludipress, Microcrystalline Cellulose (Avicel PH 102)

Coating materials: Opadry II Yellow (85G52259), Opadry II White (85G68918), Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a cool and dry place, away from light. Keep out of the reach of Children.

6.5 Nature and contents of container

Primary Packaging: Alu-Alu Blister. Secondary Packaging: Paper board carton.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

Corporate Office: Beacon Business Center, 9/B/2, Toyenbee Circular Road, Motijheel, Dhaka-1223, Bangladesh. Tel: +880-2-5716371-76, Fax: 880-2-57165379. E-mail: beacon@beaconpharma.com.bd, Website: www.beaconpharma.com.bd

Factory: Bhaluka, Mymensingh, Bangladesh

8. Marketing authorization Number

H2022/CTD8647/18827

9. Date of first authorization/renewal of the authorization

2022 August 02

10. Date of revision of the text

2022 August 02