

SUMMARY PRODUCT CHARACTERISTICS

1. Name of the medicinal product:

GALAXY'S TRELAZ 100

Trelagliptin Tablets 100 mg

2. Qualitative and Quantitative composition:

Composition:

Each film coated tablet contains:

Trelagliptin Succinate 133 mg Equivalent to Trelagliptin 100 mg

Iron Oxide Red

Excipients Q. S.

3. Pharmaceutical Form:

Tablet for Oral Administration.

Brown coloured, capsule shaped, biconvex, film coated tablet having breakline on one side and plain on other side.

4. Clinical Particulars:

4.1 Therapeutic Indications:

Indicated for the treatment of 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 impairment

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 warning and precaution for use:

Provide cautions 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.

Patients who consume excessive alcohol.

MAJOR WARNINGS:

- 1) This drug may cause hypoglycaemia when used in combination with other diabetes medications, so thoroughly explain and caution the patient of such risk of hypoglycaemia when combining with other medications. There is an increased risk of hypoglycaemia 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 hypoglycaemia.
- 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 glucosurea, 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 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. This drug and GLP-1 receptor agonists both passes 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.

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 (IC₅₀ value : 500 µmol/L or higher) or showed inhibition of uptake of metformin, an organic cationic transporter-2 (OCT2) substrate (IC₅₀ 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 AUC₂₄ (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 the ability to drive and use machines:

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

4.8 Undesirable effects:

- 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%).
 - Hypersensitivity: Rash, itch.
 - Circulatory system: Atrial fibrillation
 - Liver: Elevated ALT (GLP), 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.
- 5) Administration to pregnant women, lactating women, or for gynaecological 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 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 100 mg of this drug was taken orally every day over 12 consecutive weeks and side effects did not differ from the placebo group.

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.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti- Diabetic agent

ATC code: A10BH

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 efficacy and safety

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: $p < 0.0001$).

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.

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_{τ} 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 [¹⁴C] 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, IC₅₀ value of 100 µmol/L or higher; metabolism-based inhibition, IC₅₀ values of 12 µmol/L (midazolam 1'-hydroxylation activity) and 28 µmol/L (testosterone 6β-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 (IC₅₀ value: 500 µmol/L or higher) and OCT2 (IC₅₀ 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 (C_{cr} = 50-80 mL/min), increased by 105.7% and 12.9% in 6 patients with moderate renal impairment (C_{cr} = 30-50 mL/min), increased by 201.4% and 9.1% in 6 patients with severe renal impairment (C_{cr} < 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 pharmacokinetics 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.

5.3 Pre-clinical Safety:

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 hair-less mice.

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Silicified Microcrystalline Cellulose

Lactose

Microcrystalline Cellulose

Mannitol

Crospovidone XL

Croscarmellose Sodium

Purified Talc

Colloidal Anhydrous Silica

Sodium Stearyl Fumarate

Hypromellose (HPMC E-15)

Polyethylene glycol 6000

Red Ferric Oxide

Castor Oil

6.2 Incompatibilities:

Not applicable.

6.3 Shelf Life:

24 months.

6.4 Special Precautions for storage:

Store below 30⁰ C. Protect from direct sun light, heat and moisture.

6.5 Nature and contents of container:

Blister pack of 1 x 4 Tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder:

Galaxy Pharmaceutical Limited

Nairobi, Kenya

8. Marketing Authorization Number:

Not Applicable

9. Date of first Authorization /renewal of the authorization:

Not Applicable

10. Date of revision of text:

Not Applicable