Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

TRULI-1 50MG TABLETS

2. Qualitative and quantitative composition:

Each film coated tablet contains:

Trelagliptin Succinate .....66.5 mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

Yellow coloured, circular shaped, biconvex, film coated tablet, plain on both sides.

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 ex- cretions 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.

Method of administration

Oral use.

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

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 to3

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 trelagliptinon 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 Fertility, 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 shouldnot 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

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 may 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 properties

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

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: $p < 0.0001$).

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.

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 break- fast (on day 1) and once daily 30 minutes before breakfast for 11 days (from day 4 to 14), the mean (S.D.) Cmax 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.) Cmax and AUCτ 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 Cmax 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 trelagliptinat 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 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 (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, AUClast and Cmax 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 Cmax 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 Cmax of trelagliptin between Japanese and Caucasian

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 max- imum 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 AUC24 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 AUC24 (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 AUC24 (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, Microcrystalline Cellulose, Mannitol Lactose, crospovidone XL, Purified Talc, Colloidal anhydrous Silica, Sodium stearyl Fumarate, Hypromellose (HPMC E-15), Polyethylene glycol 6000,Yellow Ferric Oxide, Castor OIL

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage:
Store below 30°C. Protect from direct sunlight, 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 and manufacturing site addresses

Marketing authorization holder:
Company) Name: Surgilinks Limited
Address: Surgilinks Building Mombasa Road; 14461-00800. Nairobi
Country: KENYA
Telephone: **020651465/6/7/8**
Telefax: **651469**
E-Mail: registration@surgilinksltd.com
Manufacturing site address:
Company name: QUESTA
CARE LTD
Address:PLOT. NO. 209/7184, HOMABAY ROAD TERMINUS (GATE No. 19), INDUSTRIAL AREA, P.O BOX 14461-00800 NAIROBI.
Country:KENYA
Telephone:**020651465/6/7/8**
Telefax:**651469**
E-Mail:registration@surgilinksltd.com

8. Marketing authorization number
CTD9976

9. Date of first registration
03/08/2023

10. Date of revision of the text:
September 2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable