SUMMARY OF PRODUCT CHARACTERISTICS
VALSARGOOD 200 (Sacubitril/Valsartan Tablets 97 mg/103 mg)

1. NAME OF THE MEDICINAL PRODUCT

VALSARGOOD 200 (Sacubitril 97 mg / Valsartan 103 mg Film-Coated Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains sacubitril 97 mg and valsartan 103 mg (as a sodium salt complex).

Excipients with known effect:

This medicine contains less than 1 mmol sodium (23 mg) per 97 mg/103 mg dose, that is to say essentially 'sodium-free'.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult heart failure

VALSARGOOD 200 is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Paediatric heart failure

VALSARGOOD 200 is indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction.

4.2 Posology and method of administration

General considerations

VALSARGOOD 200 must not be co-administered with an ACE inhibitor or another ARB. It must not be started until at least 36 hours after discontinuing ACE inhibitor therapy, due to the risk of angioedema. If a dose is missed, the patient should take the next dose at the scheduled time.

The valsartan in VALSARGOOD 200 is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in VALSARGOOD 200 are equivalent to 40 mg, 80 mg and 160 mg of valsartan in other formulations, respectively.

Adult heart failure

Recommended starting dose: one tablet of 49 mg/51 mg sacubitril/valsartan twice daily, except in the situations below. Dose should be doubled at 2–4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated. If tolerability issues arise (SBP ≤95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down-titration or discontinuation of VALSARGOOD 200 is recommended.

Patients not currently taking an ACE inhibitor or ARB, or taking low doses: a starting dose of 24 mg/26 mg twice daily with slow dose titration (doubling every 3–4 weeks) is recommended.

Paediatric heart failure (≥1 year)

The recommended dose should be taken orally twice daily and increased every 2–4 weeks to the target dose, as tolerated. VALSARGOOD 200 film-coated tablets are not suitable for children weighing less than 40 kg; granules are available for these patients. Half the starting dose is recommended in: patients not currently taking an ACE inhibitor or ARB; patients with renal impairment (eGFR <60 ml/min/1.73 m²); and patients with moderate hepatic impairment. The safety and efficacy in children aged below 1 year have not been established.

Special populations

Elderly: dose should be in line with the patient's renal function. Renal impairment: no dose adjustment in mild impairment (eGFR 60–90 ml/min/1.73 m²); half starting dose for moderate impairment (eGFR 30–60); use with

caution and half starting dose for severe impairment (eGFR <30); no experience in end-stage renal disease — not recommended. Hepatic impairment: no dose adjustment in mild impairment (Child-Pugh A); use with caution and half starting dose in moderate impairment (Child-Pugh B); contraindicated in severe impairment (Child-Pugh C).

Method of administration
Oral. May be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Concomitant use with ACE inhibitors. VALSARGOOD 200 must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary or idiopathic angioedema.
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR <60 ml/min/1.73 m²).
- Severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification).
- Second and third trimesters of pregnancy.

4.4 Special warnings and precautions for use

Dual blockade of RAAS
The combination of sacubitril/valsartan with an ACE inhibitor is contraindicated due to increased risk of angioedema. VALSARGOOD 200 must not be initiated until 36 hours after the last dose of ACE inhibitor therapy. If VALSARGOOD 200 is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of VALSARGOOD 200. The combination with direct renin inhibitors such as aliskiren is not recommended and is contraindicated in diabetes mellitus or renal impairment (eGFR <60 ml/min/1.73 m²). VALSARGOOD 200 contains valsartan and must not be co-administered with another ARB.

Hypotension
Treatment should not be initiated unless SBP is ≥100 mmHg for adult patients or ≥5th percentile SBP for the age of the paediatric patient. Blood pressure should be monitored routinely during initiation and dose titration. Symptomatic hypotension is more likely if the patient has been volume-depleted (e.g. by diuretics, dietary salt restriction, diarrhoea or vomiting). Sodium and/or volume depletion should be corrected before starting treatment.

Renal impairment
Renal function should always be assessed in heart failure patients. There is very limited clinical experience in severe renal impairment (eGFR <30 ml/min/1.73 m²) and no experience in end-stage renal disease; use is not recommended in end-stage renal disease. Use of VALSARGOOD 200 may be associated with decreased renal function; down-titration should be considered if clinically significant renal function decrease occurs.

Hyperkalaemia
Treatment should not be initiated if serum potassium is >5.4 mmol/l (adults) or >5.3 mmol/l (paediatric). Monitoring of serum potassium is recommended, especially in patients with renal impairment, diabetes mellitus, hypoaldosteronism or on a high potassium diet or mineralocorticoid antagonists. If serum potassium >5.4 mmol/l, discontinuation should be considered.

Angioedema
If angioedema occurs, VALSARGOOD 200 must be immediately discontinued and appropriate therapy provided until complete and sustained resolution. It must not be re-administered. Angioedema involving the tongue, glottis or larynx may be fatal; airway management and adrenaline (0.3–0.5 ml of 1 mg/ml solution) should be promptly administered if required. Patients with a prior history of angioedema are at higher risk; VALSARGOOD 200 is contraindicated in patients with a known history of angioedema related to ACE inhibitor or ARB therapy or hereditary/idiopathic angioedema. Black patients have an increased susceptibility to develop angioedema.

Renal artery stenosis
VALSARGOOD 200 may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis. Monitoring of renal function is recommended.

Patients with NYHA functional classification IV
Caution should be exercised due to limited clinical experience in this population.

BNP as a biomarker

BNP is not a suitable biomarker of heart failure in patients treated with VALSARGOOD 200 because it is a neprilysin substrate. NT-proBNP is not a neprilysin substrate and is a more suitable biomarker.

Psychiatric disorders

Psychiatric events such as hallucinations, paranoia and sleep disorders, in the context of psychotic events, have been associated with sacubitril/valsartan use. If a patient experiences such events, discontinuation should be considered.

CSF amyloid-β findings

Administration of sacubitril/valsartan to healthy subjects was associated with an increase in CSF Aβ1-38 compared to placebo; there were no changes in CSF Aβ1-40 and 1-42 concentrations. The clinical relevance of this finding is not known.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per 97 mg/103 mg dose and is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

ACE inhibitors (contraindicated):

Concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. 36-hour washout required in both directions.

Aliskiren (contraindicated in diabetes/renal impairment; not recommended in others):

Higher frequency of hypotension, hyperkalaemia and decreased renal function.

Other ARBs (not recommended):

VALSARGOOD 200 contains valsartan; co-administration with another ARB must be avoided.

OATP1B1/OATP1B3 substrates (statins):

Sacubitril inhibits OATP1B1 and OATP1B3 transporters. VALSARGOOD 200 may increase the systemic exposure of statin substrates (e.g. co-administration increased atorvastatin Cmax by up to 2-fold and AUC by up to 1.3-fold). Caution should be exercised.

PDE5 inhibitors (sildenafil and others):

Addition of a single sildenafil dose to steady-state sacubitril/valsartan was associated with a significantly greater blood pressure reduction. Caution when initiating PDE5 inhibitors.

Potassium-raising agents:

Potassium-sparing diuretics, mineralocorticoid antagonists, potassium supplements, heparin — may lead to increases in serum potassium and creatinine. Monitoring recommended.

NSAIDs/COX-2 inhibitors:

In elderly, volume-depleted or renally compromised patients, concomitant use may increase risk of worsening renal function. Monitoring recommended.

Lithium (not recommended):

Reversible increases in serum lithium concentrations and toxicity reported. If combination is necessary, careful monitoring of serum lithium levels is required.

Furosemide:

Co-administration reduced Cmax and AUC of furosemide by 50% and 28%, respectively. Urinary excretion of sodium was transiently reduced.

Metformin:

Reduced Cmax and AUC of metformin by 23%. Clinical relevance unknown; evaluate clinical status of patient when initiating VALSARGOOD 200.

No clinically meaningful interaction with: digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol or levonorgestrel/ethinyl estradiol.

4.6 Fertility, pregnancy and lactation

Pregnancy

Use of VALSARGOOD 200 is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters. Exposure to ARBs during the second and third trimesters is known to induce foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Should exposure have occurred from the second trimester, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ARBs should be closely observed for hypotension. Animal studies with sacubitril/valsartan have shown reproductive toxicity.

Breast-feeding
Sacubitril and valsartan were excreted in the milk of lactating rats. Because of the potential risk for adverse reactions in breast-fed newborns/infants, VALSARGOOD 200 is not recommended during breast-feeding.

Fertility
No impairment of fertility was demonstrated in male and female rat studies.

4.7 Effects on ability to drive and use machines
VALSARGOOD 200 has a minor influence on the ability to drive and use machines. Dizziness or fatigue may occasionally occur.

4.8 Undesirable effects
Summary of the safety profile — adults
The most commonly reported adverse reactions in adult patients during treatment with sacubitril/valsartan in PARADIGM-HF were hypotension (17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%). Angioedema was reported in 0.5% of patients.

System Organ Class	Frequency	Adverse Reaction
Blood and lymphatic disorders	Common	Anaemia
Metabolism and nutrition disorders	Very common / Common / Uncommon	Hyperkalaemia (very common); hypokalaemia, hypoglycaemia (common); hyponatraemia (uncommon)
Nervous system disorders	Very common / Common	Dizziness (very common); headache, syncope (common)
Respiratory disorders	Common	Cough
Gastrointestinal disorders	Common	Diarrhoea, nausea, gastritis
Renal and urinary disorders	Very common / Common	Renal impairment (very common); renal failure (common)
Vascular disorders	Very common / Uncommon	Hypotension (very common); orthostatic hypotension (uncommon)
Immune disorders	Rare	Angioedema
Investigations	Very common	Hyperkalaemia; elevated serum creatinine
Skin disorders	Common / Uncommon	Pruritus (uncommon); rash (common)
Musculoskeletal disorders	Common	Arthralgia; back pain

Paediatric population (PANORAMA-HF)
The safety profile observed in paediatric patients aged 1 month to <18 years who received sacubitril/valsartan was similar to that observed in adult patients. Limited safety data are available in patients aged 1 month to <1 year and in paediatric patients with moderate hepatic or moderate-to-severe renal impairment.

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 National Regulatory Authority.

4.9 Overdose
Limited data are available with regard to overdose in humans. Hypotension is the most likely symptom of overdose. Symptomatic treatment should be provided. VALSARGOOD 200 is unlikely to be removed by haemodialysis due to high protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; ARBs, other combinations. ATC code: C09DX04.

Sacubitril/valsartan exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the AT1 receptor via valsartan. This enhances peptides degraded by neprilysin (e.g. natriuretic peptides), leading to vasodilation, natriuresis, diuresis, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects. Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II.

PARADIGM-HF: In this multinational, randomised, double-blind study (n=8,442), sacubitril/valsartan was superior to enalapril in reducing the composite primary endpoint of cardiovascular death or HF hospitalisation (21.8% vs 26.5%; relative risk reduction 20%; HR 0.80, p<0.0001). Both cardiovascular mortality (relative risk reduction 20%) and HF hospitalisation were reduced. All-cause mortality was significantly reduced (17.0% vs 19.8%; relative risk reduction 16%). This effect was consistently observed across subgroups including gender, age, race, NYHA class, ejection fraction, renal function, history of diabetes or hypertension, prior heart failure therapy, and atrial fibrillation.

PANORAMA-HF: A randomised, active-controlled, 52-week study in 375 paediatric heart failure patients aged 1 month to <18 years vs enalapril. The safety profile was similar to adults. A reduction in NT-proBNP was observed at weeks 4 and 12 for sacubitril/valsartan (40.2% and 49.8%) and enalapril (18.0% and 44.9%). NT-proBNP levels continued to decrease over the study duration (65.1% and 61.6% reduction at week 52, respectively).

5.2 Pharmacokinetic properties

Absorption

Following oral administration, sacubitril/valsartan dissociates into valsartan and sacubitril, which is further metabolised to the active metabolite LBQ657. Peak plasma concentrations of sacubitril, LBQ657 and valsartan are reached in approximately 1, 2 and 2 hours, respectively. Estimated oral absolute bioavailability of sacubitril and valsartan: >60% and 23%, respectively. At steady state (reached in 3 days), sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates 1.6-fold. Administration with food has no clinically significant impact.

Distribution

Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94–97%). Average apparent volume of distribution: sacubitril 103 L, valsartan 75 L. LBQ657 crosses the blood-brain barrier to a limited extent (0.28%).

Biotransformation

Sacubitril is readily converted to LBQ657 by carboxylesterases 1b and 1c; LBQ657 is not further metabolised significantly. Valsartan is minimally metabolised (approximately 20% recovered as metabolites). CYP450-mediated metabolism is minimal for both; no CYP450-based drug interactions are expected.

Elimination

52–68% of sacubitril (primarily as LBQ657) and ~13% of valsartan are excreted in urine; 37–48% of sacubitril and 86% of valsartan are excreted in faeces. Mean elimination half-lives: sacubitril ~1.43 hours, LBQ657 ~11.48 hours, valsartan ~9.90 hours. Pharmacokinetics are approximately linear over the dose range 24/26 to 97/103 mg.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Sacubitril/valsartan treatment during organogenesis was associated with increased embryofoetal lethality in rats and rabbits and cardiovascular abnormalities in rabbit foetuses. Adverse embryofoetal effects are attributed to the angiotensin receptor antagonist activity of valsartan. In juvenile rats treated with sacubitril, there was a reduction in age-related bone mass development and bone elongation at approximately 2-fold the AUC exposure based on the paediatric clinical dose of 3.1 mg/kg twice daily; the relevance to the human paediatric population is unknown. Long-term paediatric data on bone growth and fracture rates are not available. In juvenile rats treated with valsartan, persistent irreversible kidney changes (tubular nephropathy) were observed; this coincides with a period of renal development equivalent to 36–44 weeks gestation in humans, hence a clinical relevance cannot be excluded in paediatric patients less than 1 year of age.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

No.	Excipient	Specification
1	Flocel 101 (microcrystalline cellulose)	BP
2	Crospovidone XL 10	USP
3	LS HPC (LP 11) — low-substituted hydroxypropylcellulose	BP
4	Isopropyl alcohol	BP
5	Colloidal silicon dioxide	BP
6	Vivasol GF LM (sodium stearyl fumarate)	BP
7	Talcum	BP
8	Sodium stearyl fumarate	BP
9	Apicoat (titanium dioxide) — tablet coat	BP
10	Methylene dichloride	BP

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store in a dry place below 30°C. Protect from light. Keep out of the reach and sight of children.

6.5 Nature and contents of container
10 tablets packed in one ALU-ALU blister; 3 such blisters packed in one carton with package insert. Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling
No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
ZAIN PHARMA LTD.
Plot No. 209/13741, Colchester Park,
Go-Down No. 1, 2, 3, Off Mombasa Road,
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P.O. Box: 100167-00101, Nairobi, Kenya.

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