SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ARNISTO 50 (Sacubitril 24.3 mg and Valsartan 25.7 mg Tablets)

ARNISTO 100 (Sacubitril 48.6 mg and Valsartan 51.4 mg Tablets)

ARNISTO 200 (Sacubitril 97.2 mg and Valsartan 102.8 mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARNISTO 50: Each film-coated tablet contains Sacubitril 24.3 mg and Valsartan 25.7 mg as Sacubitril Valsartan Sodium Salt Complex.

ARNISTO 100: Each film-coated tablet contains Sacubitril 48.6 mg and Valsartan 51.4 mg as Sacubitril Valsartan Sodium Salt Complex.

ARNISTO 200: Each film-coated tablet contains Sacubitril 97.2 mg and Valsartan 102.8 mg as Sacubitril Valsartan Sodium Salt Complex.

Excipients: Q.S. Colour: Ferric Oxide Black USP-NF, Ferric Oxide Red USP-NF and Titanium Dioxide BP.

Excipients with known effect: None of the excipients have any pharmacological effects.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

ARNISTO 50: Peach coloured, oval shaped, flat face bevelled edge (FFBE) film-coated tablet, having one side break line and the other side plain.

ARNISTO 100: Yellow coloured, oval shaped, flat face bevelled edge (FFBE) film-coated tablet, having one side break line and the other side plain.

ARNISTO 200: Brick red, oval shaped, biconvex, film-coated tablets, having both sides plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Arnisto is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction, and in paediatric

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

4.2 Posology and method of administration

Adult heart failure

The recommended starting dose of Arnisto is one tablet of 49 mg/51 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient.

If patients experience tolerability issues (systolic blood pressure [SBP] < 95 mmHg, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down-titration or discontinuation of Arnisto is recommended.

In the PARADIGM-HF study, Arnisto was administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB. There is limited experience in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products; therefore a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3-4 weeks) is recommended in these patients.

Treatment should not be initiated in patients with serum potassium level > 5.4 mmol/l or with SBP < 100 mmHg. A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP 100 to 110 mmHg.

Paediatric heart failure

The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient. Arnisto 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 who have not been taking an ACE inhibitor or an ARB or have been taking low doses of these medicinal products, patients who have renal impairment (estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2), and patients who have moderate hepatic impairment.

Table 1 – Recommended dose titration (twice daily):

Patient weight	Half the starting dose	Starting dose	Intermediate dose	Target dose
Paediatric patients < 40 kg	0.8 mg/kg	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Paediatric patients ≥ 40 kg, < 50 kg	0.8 mg/kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg
Paediatric patients ≥ 50 kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg	97 mg/103 mg

Special populations

Elderly: The dose should be in line with the renal function of the elderly patient.

Renal impairment: No dose adjustment is required in patients with mild (eGFR 60-90 ml/min/1.73 m^2) renal impairment. Half of the starting dose should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2). There is very limited clinical experience in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2); Arnisto should be used with caution in these patients and half of the starting dose is recommended. There is no experience in patients with end-stage renal disease and use of Arnisto is not recommended.

Hepatic impairment: No dose adjustment is required when administering Arnisto to patients with mild hepatic impairment (Child-Pugh A classification). There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range; Arnisto should be used with caution in these patients and half of the starting dose is recommended. Arnisto is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification).

Paediatric population: The safety and efficacy of Arnisto in children aged below 1 year have not been established.

Method of administration

Oral use. Arnisto may be administered with or without food. The tablets must be swallowed with a glass of water. Splitting or crushing of the tablets is not recommended.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Concomitant use with ACE inhibitors. Arnisto 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 m^2).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimesters of pregnancy.

4.4 Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

The combination of sacubitril/valsartan with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with sacubitril/valsartan is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan. The combination of sacubitril/valsartan with direct renin inhibitors such as aliskiren is not recommended and is contraindicated in patients with diabetes mellitus or renal impairment (eGFR < 60 ml/min/1.73 m^2). Arnisto contains valsartan and therefore should not be co-administered with another ARB-containing medicinal product.

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. Cases of symptomatic hypotension have been reported, especially in patients ≥ 65 years old, patients with renal disease and patients with low SBP (< 112 mmHg). Blood pressure should be monitored routinely when initiating therapy or during dose titration. If hypotension occurs,

temporary down-titration or discontinuation is recommended, along with correction of volume depletion where relevant.

Renal impairment

Evaluation of patients with heart failure should always include assessment of renal function. Patients with mild and moderate renal impairment are more at risk of developing hypotension. There is very limited clinical experience in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2), who may be at greatest risk of hypotension. Use in end-stage renal disease is not recommended.

Worsening renal function

Use of sacubitril/valsartan may be associated with decreased renal function; the risk may be increased by dehydration or concomitant NSAID use. Down-titration should be considered in patients who develop a clinically significant decrease in renal function.

Hyperkalaemia

Treatment should not be initiated if serum potassium is > 5.4 mmol/l (adults) or > 5.3 mmol/l (paediatric patients). Monitoring of serum potassium is recommended, especially in patients with risk factors. Discontinuation should be considered if hyperkalaemia becomes clinically significant.

Angioedema

Angioedema has been reported in patients treated with sacubitril/valsartan. If angioedema occurs, sacubitril/valsartan should be immediately discontinued and appropriate therapy and monitoring provided until complete resolution; it must not be re-administered. Angioedema associated with laryngeal oedema may be fatal. Black patients have an increased susceptibility to develop angioedema. Intestinal angioedema has also been reported with angiotensin II receptor antagonists.

Patients with renal artery stenosis

Sacubitril/valsartan may increase blood urea and serum creatinine levels 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.

B-type natriuretic peptide (BNP)

BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because it is a neprilysin substrate.

Psychiatric disorders

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

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions resulting in a contraindication

ACE inhibitors: Concomitant use with sacubitril/valsartan is contraindicated due to increased risk of angioedema; a 36-hour washout is required in either direction.

Aliskiren: Concomitant use is contraindicated in patients with diabetes mellitus or renal impairment (eGFR < 60 ml/min/1.73 m^2), and combination with direct renin inhibitors is not recommended generally due to increased risk of hypotension, hyperkalaemia and decreased renal function.

Interactions resulting in concomitant use not being recommended

Sacubitril/valsartan should not be co-administered with another ARB-containing medicinal product.

Interactions requiring precautions

OATP1B1 and OATP1B3 substrates (e.g. statins): Sacubitril inhibits these transporters and may increase systemic exposure of statins; co-administration increased atorvastatin Cmax up to 2-fold and AUC up to 1.3-fold. No clinically relevant interaction was observed with simvastatin.

PDE5 inhibitors, including sildenafil: Co-administration was associated with significantly greater blood pressure reduction; caution should be

exercised when initiating sildenafil or another PDE5 inhibitor in patients treated with sacubitril/valsartan.

Potassium-sparing diuretics, mineralocorticoid antagonists, potassium supplements, salt substitutes and heparin: May increase serum potassium and serum creatinine; monitoring is recommended.

NSAIDs, including selective COX-2 inhibitors: May increase risk of worsening renal function, particularly in elderly, volume-depleted, or renally impaired patients; renal function monitoring is recommended.

Lithium: Reversible increases in serum lithium and toxicity have been reported with ACE inhibitors or ARBs, including sacubitril/valsartan; this combination is not recommended, and careful monitoring is required if necessary.

Furosemide: Co-administration reduced Cmax and AUC of furosemide by 50% and 28% respectively, without a relevant change in urine volume.

Nitrates, e.g. nitroglycerine: No interaction with blood pressure reduction was observed; a treatment difference of 5 bpm in heart rate was noted. In general, no dose adjustment is required.

OATP and MRP2 transporters: Co-administration with inhibitors such as rifampicin, ciclosporin, tenofovir, cidofovir, or ritonavir may increase systemic exposure of LBQ657 or valsartan; appropriate care is advised.

Metformin: Co-administration reduced Cmax and AUC of metformin by 23%; clinical relevance is unknown, and clinical status should be evaluated when initiating therapy.

No significant interaction: No clinically meaningful interaction was observed with digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol, or a combination of levonorgestrel/ethinyl estradiol.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments with an established safety profile in pregnancy. When pregnancy is diagnosed, ARB treatment should be stopped immediately. Exposure to ARBs during the second and third

trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). There are no data from the use of sacubitril/valsartan in pregnant women; animal studies have shown reproductive toxicity.

Breast-feeding

Limited data show that sacubitril and its active metabolite LBQ657 are excreted in human milk in very low amounts. Valsartan was under the limit of detection. Because of the potential risk of adverse reactions in breast-fed newborns/infants, Arnisto is not recommended during breast-feeding.

Fertility

There are no available data on the effect of sacubitril/valsartan on human fertility. No impairment of fertility was demonstrated in studies in male and female rats.

4.7 Effects on ability to drive and use machines

Sacubitril/valsartan has a minor influence on the ability to drive and use machines. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in adults during treatment with sacubitril/valsartan were hypotension (17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%). Angioedema was reported in 0.5% of patients treated with sacubitril/valsartan.

Tabulated list of adverse reactions

Adverse reactions are ranked by System Organ Class and frequency, using the convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (frequency cannot be estimated from the available data).

System organ class	Preferred term	Frequency category
Blood and lymphatic system disorders	Anaemia	Common
Immune system disorders	Hypersensitivity	Uncommon

Metabolism and nutrition disorders	Hyperkalaemia	Very common
	Hypokalaemia	Common
	Hypoglycaemia	Common
	Hyponatraemia	Uncommon
Psychiatric disorders	Hallucinations	Rare
	Sleep disorders	Rare
	Paranoia	Very rare
Nervous system disorders	Dizziness	Common
	Headache	Common
	Syncope	Common
	Dizziness postural	Uncommon
	Myoclonus	Not known
Ear and labyrinth disorders	Vertigo	Common
Vascular disorders	Hypotension	Very common
	Orthostatic hypotension	Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Diarrhoea	Common
	Nausea	Common
	Gastritis	Common
	Intestinal angioedema	Very rare
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Uncommon
	Angioedema	Uncommon
Renal and urinary disorders	Renal impairment	Very common
	Renal failure (renal failure, acute renal failure)	Common
General disorders and administration site conditions	Fatigue	Common
	Asthenia	Common

Description of selected adverse reactions

Angioedema: In PARADIGM-HF, angioedema was reported in 0.5% of patients treated with sacubitril/valsartan compared with 0.2% treated with enalapril. A higher incidence was observed in Black patients (2.4% vs 0.5%).

Hyperkalaemia and serum potassium: In PARADIGM-HF, hyperkalaemia and serum potassium ≥5.4 mmol/l were reported in 11.6% and 19.7% of sacubitril/valsartan-treated patients, and 14.0% and 21.1% of enalapril-treated patients, respectively.

Blood pressure: In PARADIGM-HF, hypotension and clinically relevant low SBP (<90 mmHg with a decrease from baseline of ≥20 mmHg) were reported in 17.6% and 4.76% of sacubitril/valsartan-treated patients, compared with 11.9% and 2.67% of enalapril-treated patients.

Renal impairment: In PARADIGM-HF, renal impairment was reported in 10.1% of sacubitril/valsartan-treated patients and 11.5% of enalapril-treated patients.

Paediatric population: In the PANORAMA-HF study, the safety profile in paediatric patients aged 1 month to 18 years was similar to that observed in adults. Safety data in patients aged 1 month to 1 year, and in those with moderate hepatic impairment or moderate-to-severe renal impairment, was limited.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS):

https://pv.pharmacyboardkenya.org

4.9 Overdose

Limited data are available with regard to overdose in humans. A single dose of 583 mg sacubitril/617 mg valsartan and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) were studied in healthy adult volunteers and were well tolerated. Hypotension is the most likely symptom of overdose due to the blood pressure lowering effects of sacubitril/valsartan. Symptomatic treatment should be provided. The medicinal product 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; angiotensin II receptor blockers (ARBs), other combinations.

ATC code: C09DX04.

Mechanism of action

Sacubitril/valsartan exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase, NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits in heart failure patients are attributed to enhancement of peptides degraded by neprilysin, such as natriuretic peptides, by LBQ657, together with simultaneous inhibition of angiotensin II effects by valsartan. Natriuretic peptides activate membrane-bound guanylyl cyclase-coupled receptors, increasing cGMP, which can result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, 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 by selectively blocking the AT1 receptor and inhibits angiotensin II-dependent aldosterone release, preventing sustained RAAS activation and consequent maladaptive cardiovascular remodelling.

Clinical efficacy and safety

PARADIGM-HF, the pivotal phase 3 study, was a multinational, randomised, double-blind study of 8,442 adult patients with chronic heart failure, NYHA class II-IV and reduced ejection fraction, comparing sacubitril/valsartan to enalapril in addition to other heart failure therapy. The primary endpoint was the composite of cardiovascular death or hospitalisation for heart failure. Sacubitril/valsartan was superior to enalapril, reducing the risk of cardiovascular death or heart failure hospitalisation to 21.8% compared to 26.5% for enalapril-treated patients. In the PANORAMA-HF paediatric study, a 52-week randomised, active-controlled study of 375 paediatric heart failure patients aged 1 month to 18 years compared to enalapril, reductions in NT-proBNP were observed over the study duration in both treatment arms.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril, which is further metabolised to the active metabolite Sacubitrilat. Peak plasma concentrations are reached in 2 hours, 1 hour, and 2 hours, respectively. Oral absolute bioavailability of sacubitril and valsartan is estimated to be more than 60% and 23%, respectively. Steady-state levels are reached in three days with twice-daily dosing; sacubitril and valsartan do not accumulate significantly, while Sacubitrilat accumulates 1.6-fold. Administration with food has no clinically significant impact on systemic exposure, and the product can be administered with or without food.

Distribution

Sacubitril, Sacubitrilat and valsartan are highly bound to plasma proteins (94-97%). Sacubitrilat crosses the blood-brain barrier to a limited extent (0.28). The average apparent volume of distribution of valsartan and sacubitril were 75 litres and 103 litres, respectively.

Biotransformation

Sacubitril is readily converted to Sacubitrilat by carboxylesterases 1b and 1c; Sacubitrilat is not further metabolised to a significant extent. Valsartan is minimally metabolised (about 20% of the dose recovered as metabolites). Since CYP450-enzyme-mediated metabolism of sacubitril and valsartan is minimal, co-administration with medicinal products that impact CYP450 enzymes is not expected to impact the pharmacokinetics.

Elimination

52-68% of sacubitril (primarily as Sacubitrilat) and 13% of valsartan and its metabolites are excreted in urine; 37-48% of sacubitril and 86% of valsartan and its metabolites are excreted in faeces. Sacubitril, Sacubitrilat and valsartan are eliminated from plasma with a mean elimination half-life of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

5.3 Preclinical safety data

Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β from the brain and cerebrospinal fluid (CSF). Administration of sacubitril/valsartan to healthy subjects was associated with an increase in CSF Aβ1-38 compared to placebo, with no changes in concentrations

of CSF Aβ1-40 and Aβ1-42; the clinical relevance of this finding is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients Q.S. Colour: Ferric Oxide Black USP-NF, Ferric Oxide Red USP-NF and Titanium Dioxide BP. None of the excipients have any pharmacological effects.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years from the date of manufacture.

6.4 Special precautions for storage

Do not store above 30°C. Protect from direct sunlight. Keep all medicines out of reach of children.

6.5 Nature and contents of container

Blister pack of 3 x 10s, packed in a printed unit carton along with a literature insert.

6.6 Distribution category

Prescription Only Medicine (POM).

7 Marketing Authorisation Holder

Dawa Limited,

Plot No. 78798, Baba Dogo Road, Ruaraka,

P.O. Box 16633-00620, Nairobi, Kenya.

8 Manufacturer

Ravenbhel Healthcare Pvt. Ltd.,

16-17, EPIP, SIDCO, Kartholi, Bari Brahmana,

Jammu-181133, India.

9 Marketing Authorization Numbers

H2025/CTD12549/26185

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