ARNOZA

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

Abbreviated Prescribing information for ARNOZA (Sacubitril and Valsartan tablets 50 mg, 100 mg and 200 mg) [Please refer the complete prescribing information for details].

PHARMACOLOGICAL PROPERTIES:

MECHANISM OF ACTION: Sacubitril and 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 of Sacubitril and Valsartan in heart failure patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could 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 also inhibits angiotensin II-dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodeling.

INDICATIONS: To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

DOSAGE AND ADMINISTRATION: As directed by the Physician. Tablets should be taken orally.

CONTRAINDICATION: Hypersensitivity to the active substances or to any of the excipients, Concomitant use with ACE inhibitors. Sacubitril and Valsartan 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 and cholestasis, Second and third trimester of pregnancy.

WARNINGS & PRECAUTIONS: ***Dual blockade of the renin-angiotensin-aldosterone system (RAAS):*** The combination of Sacubitril and Valsartan with an ACE inhibitor is contraindicated due to the increased risk of angioedema. ***Hypotension:*** Treatment should not be initiated unless SBP is ≥100 mmHg. As per reported data, Patients with SBP <100 mmHg were not studied. Cases of symptomatic hypotension have been reported. ***Impaired renal function:*** 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**.** ***Worsening renal function:*** Use of Sacubitril and Valsartan may be associated with decreased renal function. ***Hyperkalaemia:*** Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. ***Angioedema:*** Angioedema has been reported in patients treated with Sacubitril and Valsartan. If angioedema occurs, Sacubitril and Valsartan should be immediately discontinued. ***Patients with renal artery stenosis:*** Sacubitril and Valsartan may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. ***Patients with NYHA functional classification IV:*** Caution should be exercised when initiating Sacubitril and Valsartan in patients with NYHA. ***B-type natriuretic peptide (BNP):*** BNP is not a suitable biomarker of heart failure in patients treated with Sacubitril and Valsartan. ***Patients with hepatic impairment:*** there is limited clinical experience in patients with moderate hepatic impairment. ***Psychiatric disorders:*** Psychiatric events such as hallucinations, paranoia and sleep disorders.

DRUG INTERACTIONS: ***Interactions resulting in a contraindication:*** *ACE inhibitors:* The concomitant use of Sacubitril and Valsartan with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema**.** ***Aliskiren:*** The concomitant use of Sacubitril and Valsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or in patients with renal

impairment. ***Interactions resulting in concomitant use not being recommended;*** Sacubitril and Valsartan contains valsartan, and therefore should not be co-administered with another ARB containing product. ***Interactions requiring precautions: OATP1B1 and OATP1B3 substrates:*** According to reported study sacubitril inhibits OATP1B1 and OATP1B3 transporters. Sacubitril and Valsartan may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. ***PDE5 inhibitors including sildenafil:*** Addition of a single dose of sildenafil to Sacubitril and Valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of Sacubitril and Valsartan alone. ***Potassium*** Concomitant use of potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, and salt substitutes containing potassium or other agents (such as heparin) may lead to increases in serum potassium and to increases in serum creatinine. ***Non-steroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors:*** In elderly patients, volume-depleted patients (including those on diuretic therapy), or patients with compromised renal function, concomitant use of Sacubitril and Valsartan and NSAIDs may lead to an increased risk of worsening of renal function.. ***Lithium:*** Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. ***Furosemide:*** Co-administration of Sacubitril and Valsartan and furosemide had no effect on the pharmacokinetics of Sacubitril and Valsartan but reduced C_{max} and AUC of furosemide by 50% and 28%, respectively. ***Nitrates, e.g. nitroglycerine:*** there was no drug-drug interaction between Sacubitril and Valsartan and intravenously administered nitroglycerin with regard to blood pressure reduction. ***OATP and MRP2 transporters:*** The active metabolite of sacubitril (LBQ657) and valsartan are OATP1B1, OATP1B3, OAT1 and OAT3 substrates; valsartan is also a MRP2 substrate. Therefore, co-administration of Sacubitril and Valsartan with inhibitors may increase the systemic exposure of LBQ657 or valsartan. ***Metformin:*** Co-administration of Sacubitril and Valsartan with metformin reduced both C_{max} and AUC of metformin by 23%. The clinical relevance of these findings is unknown. ***No significant interaction:*** No clinically meaningful drug-drug interaction was observed when Sacubitril and Valsartan was co-administered with digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol or a combination of levonorgestrel/ethinyl estradiol in reported studies.

ADVERSE REACTIONS: ***Blood and lymphatic system disorders:*** Anaemia. ***Immune system disorders:*** Hypersensitivity. ***Metabolism and nutrition disorders:*** Hyperkalaemia, Hypokalaemia, Hypoglycaemia. ***Nervous system disorders:*** Dizziness, Headache, Syncope, Dizziness postural. **Ear and labyrinth disorders:** Vertigo. ***Vascular disorders:*** Hypotension, Orthostatic hypotension. ***Respiratory, thoracic and mediastinal disorders:*** Cough. ***Gastrointestinal disorders:*** Diarrhoea, Nausea, Gastritis. ***Skin and subcutaneous tissue disorders:*** Pruritus, Rash, Angioedema. ***Renal and urinary disorders:*** Renal impairment, Renal failure (renal failure, acute renal failure). ***General disorders and administration site conditions:*** Fatigue, Asthenia. ***Psychiatric disorders:*** Hallucinations, Sleep disorders, Paranoia.

MARKETED BY:

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(Additional information is available on request)