Professional information for ARNIZYD

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

ARNIZYD 26/24 film-coated tablets

ARNIZYD 51/49 film-coated tablets

ARNIZYD 103/97 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARNIZYD 26/24: Each film-coated tablet contains 24 mg sacubitril and 26 mg valsartan.

ARNIZYD 51/49: Each film-coated tablet contains 49 mg sacubitril and 51 mg valsartan.

ARNIZYD 103/97: Each film-coated tablet contains 97 mg sacubitril and 103 mg valsartan.

Excipients with known effect:

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ARNIZYD 26/24: White to off-white coloured, film-coated, oval shaped tablets, debossed with "1272" on one side and plain on other side.

ARNIZYD 51/49: Brown to dark brown coloured, film-coated, oval shaped tablets, debossed with "1273" on one side and plain on other side.

ARNIZYD 103/97: Light orange to orange coloured, film-coated, oval shaped tablets, debossed with "1274" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARNIZYD is indicated as a second-line therapy, replacing angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) for treatment of symptomatic heart failure (NYHA class II – IV) in patients with systolic dysfunction. ARNIZYD is administered in combination with other heart failure therapies as appropriate.

4.2 Posology and method of administration

Posology

The target dose of ARNIZYD is 200 mg twice daily. To avoid hypotension the recommended starting dose of ARNIZYD in patients previously using high doses of ACE or ARB is 100 mg twice daily.

A starting dose of 50 mg twice daily is recommended for patients currently taking low doses of ACE or ARB. Dose up titration by increasing the dose every 3 – 4 weeks is recommended until a dose of 200 mg twice daily is achieved with tolerance. Each dose increment should be preceded by clinical observation for hypotension and laboratory evaluation of serum potassium and renal function. ARNIZYD must not be started until 36 hours after discontinuing ACE inhibitor therapy (see section 4.3).

If patients experience tolerability issues (symptomatic hypotension, hyperkalaemia, renal dysfunction) consideration should be given to adjustment of concomitant medications, or to down-titration or discontinuation of ARNIZYD.

Special populations

Renal impairment:

ARNIZYD is contraindicated in patients with severe impaired renal function.

Hepatic impairment:

No dose adjustment is required when administering ARNIZYD to patients with mild to moderate hepatic impairment (Child-Pugh A and B classification).

No studies have been conducted in patients with severe hepatic impairment (Child-Pugh C classification). Therefore, use of ARNIZYD in these patients is not recommended (see section 5.2).

Elderly patients (older than 65 years):

Patients over the age of 65 years may have impaired renal function, therefore a lower starting dose is recommended.

Paediatric population

The safety and efficacy of ARNIZYD in paediatric patients aged below 18 years has not been established.

Method of administration

Oral use.

ARNIZYD may be administered with or without food (see section 5.2).

4.3 Contraindications

- Hypersensitivity to sacubitril, valsartan or to any of the excipients listed in section 6.1.
- Concomitant use with ACE inhibitors (see sections 4.2, 4.4 and 4.5). ARNIZYD must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy. These patients must never again be given these medicines (see section 4.4).
- Hereditary or idiopathic angioedema (see section 4.4).
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.

- Aortic valve stenosis.
- Concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with ARNIZYD may lead to toxic blood concentrations of lithium (see section 4.5).
- Concomitant use with aliskiren-containing medicines (see sections 4.4 and 4.5).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Severe hepatic impairment, biliary cirrhosis, and cholestasis (see section 4.2).
- Pregnancy and lactation (see section 4.6).
- Concomitant use of ARNIZYD with renin antagonists such as aliskiren (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving ARNIZYD, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

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

- The combination of ARNIZYD with an ACE inhibitor is contraindicated due to the increased risk of angioedema (see section 4.3). ARNIZYD must not be initiated until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment with ARNIZYD is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose of ARNIZYD (see sections 4.2, 4.3 and 4.5).
- The combination of ARNIZYD with direct renin inhibitors, such as aliskiren, is not recommended (see section 4.5). The combination of sacubitril/valsartan with aliskiren-containing medicines is contraindicated in patients with diabetes mellitus or in patients with renal impairment (eGFR < 60 mL/min/1,73 m^2) (see sections 4.3 and 4.5).

- ARNIZYD contains valsartan and therefore should not be co-administered with another ARB-containing medicine (see sections 4.2 and 4.5).

Hypotension

Treatment should not be initiated unless systolic blood pressure (SBP) is ≥ 100 mm Hg. Patients with SBP < 100 mm Hg were not studied. Cases of symptomatic hypotension have been reported in patients treated with sacubitril/valsartan during clinical studies (see section 4.8), especially in patients ≥ 65 years old, patients with renal disease and patients with low SBP (< 112 mm Hg). When initiating therapy or during dose titration with ARNIZYD, blood pressure should be monitored routinely. If hypotension occurs, temporary down-titration or discontinuation of ARNIZYD is recommended (see section 4.2). Dose adjustment of diuretics, concomitant antihypertensives and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. Symptomatic hypotension is more likely to occur if the patient has been volume-depleted, e.g. by diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Sodium and/or volume depletion should be corrected before starting treatment with ARNIZYD, however, such corrective action must be carefully weighed against the risk of volume overload.

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. There is very limited clinical experience in patients with severe renal impairment (estimated GFR < 30 mL/min/1,73 m^2) and these patients may be at greatest risk of hypotension. There is no experience in patients with end-stage renal disease and use of ARNIZYD is not recommended.

Worsening renal function

Use of ARNIZYD may be associated with decreased renal function. The risk may be further increased by dehydration or concomitant use of nonsteroidal antiinflammatory drugs (NSAIDs) (see section 4.5). Down-titration should be considered in patients who develop a clinically

significant decrease in renal function (see section 4.3).

Hyperkalaemia

Treatment should not be initiated if the serum potassium level is > 5,4 mmol/L. The use of ARNIZYD may be associated with an increased risk of hyperkalaemia, although hypokalaemia may also occur (see section 4.8). Monitoring of serum potassium is recommended, especially in patients who have risk factors such as renal impairment, diabetes mellitus or hypoaldosteronism or who are on a high potassium diet or on mineralocorticoid antagonists (see section 4.2).
Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should not be used with ARNIZYD. If patients experience clinically significant hyperkalaemia adjustment of concomitant medicines, or temporary down-titration or discontinuation is recommended. If serum potassium level is > 5,4 mmol/L, discontinuation should be considered.

Angioedema

Angioedema has been reported in patients treated with sacubitril/valsartan. If angioedema occurs, ARNIZYD should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. It must not be re-administered.
In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy, e.g. adrenaline solution 1 mg/1 mL (0,3 – 0,5 mL), and/or measures necessary to ensure a patent airway, should be promptly administered.

Patients with a prior history of angioedema were not studied. As they may be at higher risk for angioedema, caution is recommended if ARNIZYD is used in these patients. ARNIZYD is contraindicated in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy or with hereditary or idiopathic angioedema (see section 4.3).
Black patients have an increased susceptibility to develop angioedema (see section 4.8).

Patients with renal artery stenosis

ARNIZYD may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis (see section 4.3).

Patients with NYHA functional classification IV

Caution should be exercised when initiating ARNIZYD in patients with NYHA functional classification IV 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 ARNIZYD because it is a neprilysin substrate (see section 5.1).

Patients with hepatic impairment

There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with aspartate aminotransferase (AST) / alanine aminotransferase (ALT) values more than twice the upper limit of the normal range. In these patients, exposure may be increased, and safety is not established. Caution is therefore recommended when using it in these patients (see sections 4.2 and 5.2). ARNIZYD is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification) (see section 4.3).

Interactions with statins

Statins: *In vitro* data indicates that sacubitril inhibits $0ATP_1B_1$ and $0ATP_1B_3$ transporters. ARNIZYD may therefore increase the systemic exposure of $0ATP_1B_1$ and $0ATP_1B_3$ substrates such as statins.

Co-administration of ARNIZYD increased the C_{max} of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1,3-fold. Therefore, caution should be exercised upon co-administration of ARNIZYD with statins as the adverse effects of statins are dose/exposure related.

4.5 Interaction with other medicines and other forms of interaction

Interactions resulting in a contraindication

ACE inhibitors:

The concomitant use of ARNIZYD with ACE inhibitors is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema. ARNIZYD must not be started until 36 hours after taking the last dose of ACE inhibitor therapy. ACE inhibitor therapy must not be started until 36 hours after the last dose of ARNIZYD (see sections 4.2 and 4.3).

Aliskiren:

The concomitant use of ARNIZYD with aliskiren-containing medicines is contraindicated (see section 4.3). The combination of ARNIZYD with direct renin inhibitors such as aliskiren is not recommended (see section 4.4). Combination of ARNIZYD with aliskiren is potentially associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) (see sections 4.3 and 4.4).

Interactions resulting in concomitant use not being recommended

ARNIZYD contains valsartan and therefore should not be co-administered with another ARB-containing medicine (see section 4.4).

Interactions requiring precautions

$OATP_1B_1$ and $OATP_1B_3$ substrates, e.g. statins:

In vitro data indicate that sacubitril inhibits $OATP_1B_1$ and $OATP_1B_3$ transporters. ARNIZYD may therefore increase the systemic exposure of $OATP_1B_1$ and $OATP_1B_3$ substrates such as statins. Co-administration of ARNIZYD increased the C_{max} of atorvastatin and its metabolites by up to 2-fold and AUC by up to 1,3-fold. Caution should be exercised when co-administering ARNIZYD with statins. No clinically relevant interaction was observed when simvastatin and ARNIZYD were co-administered.

PDE5 inhibitors, including sildenafil:

Addition of a single dose of sildenafil to ARNIZYD at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of ARNIZYD alone. Therefore, caution should be exercised when sildenafil or another PDE5 inhibitor is initiated in patients treated with ARNIZYD.

Potassium:

Concomitant use of potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium or other medicines (such as heparin) may lead to increases in serum potassium, and to increases in serum creatinine. Monitoring of serum potassium is recommended if ARNIZYD is co-administered with these medicines (see section 4.4).

Nonsteroidal antiinflammatory 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 ARNIZYD and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying treatment in patients on ARNIZYD who are taking NSAIDs concomitantly

(see section 4.4).

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. Interactions between ARNIZYD and lithium have not been investigated. Therefore, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further.

Furosemide:

Co-administration of sacubitril/valsartan and furosemide had no effect on the pharmacokinetics of ARNIZYD but reduced C_{max} and AUC of furosemide by 50 % and 28 %, respectively. While there was no relevant change in urine volume, the urinary excretion of sodium was reduced within 4 hours and 24 hours after co-administration.

Nitrates, e.g. nitroglycerine:

There is no interaction between ARNIZYD and intravenously administered nitroglycerine with regard to blood pressure reduction. Co-administration of nitroglycerine and ARNIZYD is associated with a treatment difference of 5 bpm in heart rate compared to the administration of nitroglycerine alone. A similar effect on the heart rate may occur when ARNIZYD is co-administered with sublingual, oral or transdermal nitrates. In general, no dose adjustment is required.

OATP and MRP2 transporters:

The active metabolite of sacubitril (LBQ657) and valsartan are $OATP_1B_1$, $OATP_1B_3$, OAT_1 and OAT_3 substrates; valsartan is also an MRP2 substrate. Therefore, co-administration of ARNIZYD with inhibitors of $OATP_1B_1$, $OATP_1B_3$, OAT3 (e.g. rifampicin, ciclosporin), OAT_1 (e.g. tenofovir, cidofovir) or MRP_2 (e.g. ritonavir) may increase the systemic exposure of LBQ657 or valsartan.

Appropriate care should be exercised when initiating or ending concomitant treatment with such medicines.

Metformin:

Co-administration of sacubitril/valsartan with metformin reduced both C_{max} and AUC of metformin by 23 %. The clinical relevance of these findings is unknown. Therefore, when initiating therapy with ARNIZYD in patients receiving metformin, the clinical status of the patient should be evaluated.

No significant interaction:

No clinically meaningful interaction was observed when ARNIZYD was co-administered with digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol or a combination of levonorgestrel/ethinylestradiol.

No interaction is expected with atenolol, indometacin, glyburide, or cimetidine.

CYP450 interactions:

In vitro metabolism studies indicate that the potential for CYP450 based interactions is low since there is limited metabolism of ARNIZYD via the CYP450 enzymes: ARNIZYD does not induce or inhibit CYP450 enzymes.

4.6 Fertility, pregnancy and lactation

ARNIZYD is contraindicated in pregnancy and lactation.

Safety in pregnancy and lactation has not been established (see section 4.3).

When pregnancy is planned or confirmed ARNIZYD should be discontinued. Medicines affecting the renin-angiotensin system, such as ARNIZYD, can cause embryonal toxicity, fetal and neonatal morbidity and mortality, when administered to pregnant women.

Breastfeeding

It is not known whether ARNIZYD is excreted in human milk. The components of ARNIZYD, sacubitril and valsartan, were excreted in the milk of lactating rats. Because of the potential risk for adverse reactions in breastfed newborns/infants, it is contraindicated during breastfeeding (see section 4.3).

Fertility

There are no available data on the effect of ARNIZYD on human fertility. No impairment of fertility was demonstrated in studies with it in male and female rats.

4.7 Effects on ability to drive and use machines

ARNIZYD 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

Immune system disorders

Less frequent: hypersensitivity

Blood and lymphatic system disorders

Frequent: anaemia

Metabolism and nutrition disorders

Frequent: hyperkalaemia, hypokalaemia, hypoglycaemia

Nervous system disorders

Frequent: dizziness, headache

Less frequent: postural dizziness

Ear and labyrinth disorders

Frequent: vertigo

Vascular disorders

Frequent: hypotension, syncope, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Frequent: cough

Gastrointestinal disorders

Frequent: diarrhoea, nausea, gastritis

Skin and subcutaneous tissue disorders

Less frequent: pruritus, rash, angioedema

Renal and urinary disorders

Frequent: renal impairment, renal failure (including acute renal failure)

General disorders and administration site conditions

Frequent: fatigue, asthenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ARNIZYD is important. It allows continued monitoring of the benefit/risk balance of ARNIZYD. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Hypotension is the most likely symptom of overdose due to the blood pressure-lowering effects of ARNIZYD.

Symptomatic treatment should be provided.

ARNIZYD is unlikely to be removed by haemodialysis due to high protein binding (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.6 Others.

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 (AT_1) receptor via valsartan. The complementary cardiovascular benefits of sacubitril/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 antihypertrophic and antifibrotic effects.

Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively

blocking the AT_1 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 remodelling.

Pharmacodynamic effects

The pharmacodynamic effects of sacubitril/valsartan were evaluated after single and multiple dose administrations in healthy subjects and in patients with heart failure and are consistent with simultaneous neprilysin inhibition and RAAS blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of sacubitril/valsartan resulted in an initial increase in natriuresis, increased urine cGMP, and decreased plasma levels of mid-regional pro-atrial natriuretic peptide (MR-proANP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP) compared to valsartan. In a 21-day study in heart failure with reduced ejection fraction (HFrEF) patients, sacubitril/valsartan significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1 compared to baseline. The AT_1 receptor was also blocked as evidenced by increased plasma renin activity and plasma renin concentrations. In the PARADIGM-HF study, sacubitril/valsartan decreased plasma NT-proBNP and increased plasma BNP and urine cGMP compared with enalapril. BNP is not a suitable biomarker of heart failure in patients treated with sacubitril/valsartan because BNP is a neprilysin substrate (see section 4.4). NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

In a thorough QTc clinical study in healthy male subjects, single doses of sacubitril/valsartan 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg valsartan had no effect on cardiac repolarisation.

Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF). Administration of sacubitril/valsartan 194 mg sacubitril/206 mg

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration, sacubitril/valsartan dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolised to the active metabolite LBQ657. These reach peak plasma concentrations in 0,5 hours, 3 hours and 1,5 hours, respectively. The oral absolute bioavailability of sacubitril and valsartan is estimated to be more than 60 % and 23 %, respectively. Following twice daily dosing of sacubitril/valsartan, steady-state levels of sacubitril, LBQ657 and valsartan are reached in three days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates 1,6-fold.
Administration with food has no clinically significant impact on the systemic exposures of sacubitril, LBQ657 and valsartan. Sacubitril/valsartan can be administered with or without food.

Distribution

Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94 – 97 %). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood-brain barrier to a limited extent (0,28 %). The average apparent volume of distribution of valsartan and sacubitril were 107,8 litres to 157,4 litres, respectively.

Biotransformation

Sacubitril is readily converted to LBQ657 by carboxylesterases 1b and 1c; LBQ657 is not further metabolised to a significant extent. Valsartan is minimally metabolised, as only about 20 % of the dose is recovered as metabolites. A hydroxyl metabolite of valsartan has been identified in plasma at low concentrations (< 10 %).

Since CYP450 enzyme-mediated metabolism of sacubitril and valsartan is minimal, co-administration with medicines that impact CYP450 enzymes is not expected to impact the pharmacokinetics.

In vitro metabolism studies indicate that potential for CYP450 based medicine interactions is low since there is limited metabolism of sacubitril/valsartan via CYP450 enzymes. Sacubitril/valsartan does not induce or inhibit CYP450 enzymes.

Elimination

Following oral administration, 52 – 68 % of sacubitril (primarily as LBQ657) and ~13 % of valsartan and its metabolites are excreted in urine; 37 – 48 % of sacubitril (primarily as LBQ657) and 86 % of valsartan and its metabolites are excreted in faeces.

Sacubitril, LBQ657 and valsartan are eliminated from plasma with a mean elimination half-life ($T_{½}$) of approximately 1,43 hours, 11,48 hours and 9,90 hours, respectively.

Linearity/non-linearity

The pharmacokinetics of sacubitril, LBQ657 and valsartan were approximately linear over a sacubitril/valsartan dose range of 24 mg sacubitril/26 mg valsartan to 97 mg sacubitril/103 mg valsartan.

Special populations

Elderly patients (aged over 65 years)

LBQ657 and valsartan exposure are increased in subjects over 65 years of age by 42 % and 30 %, respectively, compared to younger subjects (see section 4.2).

Paediatric patients (aged below 18 years)

Sacubitril valsartan sodium hydrate has not been studied in paediatric patients.

Impaired renal function

A correlation was observed between renal function and systemic exposure to LBQ657 in patients with mild to severe renal impairment. The exposure of LBQ657 in patients with moderate (30 mL/min/1,73 m^2 ≤ eGFR < 60 mL/min/1,73 m^2) and severe renal impairment (15 mL/min/1,73 m^2 ≤ eGFR < 30 mL/min/1,73 m^2) was 2,7-fold higher compared to patients with mild renal impairment (60 mL/min/1,73 m^2 ≤ eGFR < 90 mL/min/1,73 m^2), the largest group of patients enrolled in PARADIGM-HF). The exposure of valsartan was similar in patients with moderate and severe renal impairment compared to patients with mild renal impairment. No studies have been performed in patients undergoing dialysis. However, LBQ657 and valsartan are highly bound to plasma protein and therefore unlikely to be effectively removed by dialysis.

Impaired hepatic function

In patients with mild to moderate hepatic impairment, the exposures of sacubitril increased by 1,5- and 3,4- fold, LBQ657 increased by 1,5- and 1,9-fold, and valsartan increased by 1,2-fold and 2,1-fold, respectively, compared to matching healthy subjects. No dosage adjustments are recommended when administering sacubitril valsartan sodium hydrate to patients with mild to moderate hepatic impairment (Child-Pugh A and B classification) including patients with biliary obstructive disorders. Sacubitril valsartan sodium hydrate has not been studied in patients with severe hepatic impairment. Therefore, its use is not recommended in patients with severe hepatic impairment.

Effect of gender

The pharmacokinetics of sacubitril/valsartan (sacubitril, LBQ657 and valsartan) are similar between male and female subjects.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide (E551)

Crospovidone (E1202)

Hydroxypropyl cellulose (E463)

Microcrystalline cellulose [E460(i)]

Sodium stearyl fumarate.

Film coating:

ARNIZYD 26/24: Opadry White [containing hypromellose (E464), macrogol (E1521) and titanium dioxide (E171)].

ARNIZYD 51/49: Opadry Brown [containing hypromellose (E464), iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172), macrogol (E1521) and titanium dioxide (E171)].

ARNIZYD 103/97: Opadry Orange [containing FD&C Blue (E132), FD&C Red (E129), FD&C Yellow (E102), hypromellose (E464), macrogol (E1521) and titanium dioxide (E171)].

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

6.5 Nature and contents of container

Alu-OPA/MAF/PVC blister strips in a carton containing 30 or 60 tablets.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

ARNIZYD 26/24: 55/7.6/0497

ARNIZYD 51/49: 55/7.6/0498

ARNIZYD 103/97: 55/7.6/0499

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

24 June 2025

10. DATE OF REVISION OF THE TEXT

Not applicable.