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

ARNOZA D

WARNING

FETAL TOXICITY

- When pregnancy detected, discontinue Dapagliflozin, Sacubitril and Valsartan tablets as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

1. Generic Name

Dapagliflozin and Sacubitril Valsartan Tablets (5mg + 50mg/5mg+ 100mg/5mg+ 200mg).

2. Qualitative and quantitative Composition:

ARNOZA D (5+50)

Each film coated tablet contains:

Dapagliflozin Propanediol USP Equivalent to

Dapagliflozin…….5 mg

Sacubitril and Valsartan as sodium salt complex……. 50 mg (24 mg + 26 mg)

Excipients……. q.s.

Colours: Ferric Oxide USP NF Red, Ferric Oxide USP NF Black & Titanium Dioxide IP

The excipients used are Colloidal Silicon dioxide, Microcrystalline Cellulose, Povidone K-30, Isopropyl Alcohol, Microcrystalline Cellulose, Crospovidone, , Purified Talc, Calcium Stearate, Hydroxy propyl methyl cellulose, Polyethylene Glycol, Titanium Dioxide, Ferric Oxide Red, Ferroso Ferric Oxide USP.

ARNOZA D (5+100)

Each film coated tablet contains:

Dapagliflozin Propanediol USP Equivalent to

Dapagliflozin…….5 mg

Sacubitril and Valsartan as sodium salt complex……. 100 mg (49 mg + 51 mg)

Excipients……. q.s.

Colours: Ferric Oxide USP NF Red, Ferric Oxide USP NF Yellow & Titanium Dioxide IP

The excipients used are Colloidal Silicon dioxide, Microcrystalline Cellulose, Povidone K-30, Isopropyl Alcohol, Microcrystalline Cellulose, Crospovidone, , Purified Talc, Calcium Stearate, Hydroxy propyl methyl cellulose, Polyethylene Glycol, Talc, Titanium Dioxide, Ferric Oxide Red, Ferric Oxide Yellow.

ARNOZA D (5+200)

Each film coated tablet contains:

Dapagliflozin Propanediol USP Equivalent to

Dapagliflozin…….5 mg

Sacubitril and Valsartan as sodium salt complex……. 200 mg (97 mg + 103 mg)

Excipients……. q.s.

Colours: Ferric Oxide USP NF Red & Titanium Dioxide IP

The excipients used are Colloidal Silicon dioxide, Microcrystalline Cellulose, Povidone K-30, Isopropyl Alcohol, Microcrystalline Cellulose, Crospovidone, Purified Talc, Calcium Stearate, Titanium Dioxide, Red Iron Oxide

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: 5mg + 50mg/5mg+ 100mg/5mg+ 200mg

4. Clinical particulars

4.1. Therapeutic indication

It is indicated in patients with heart failure with reduced ejection fraction.

4.2. Posology and method of administration

Posology

The recommended dose is one tablet twice a day. Each film coated tablet contains a fixed dose of Dapagliflozin and Sacubitril Valsartan.

Method of administration

It should be given orally one tablet twice a day with or without meal.

4.3. Contraindications

- In patients with hypersensitivity to any component of Dapagliflozin, Sacubitril and Valsartan
- In patients with a history of angioedema related to previous ACE inhibitor or ARB therapy
- With concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor.
- With concomitant use of aliskiren in patients with diabetes.
- History of a serious hypersensitivity reaction to Dapagliflozin, such as anaphylactic reactions or angioedema.
- Patients who are being treated for glycemic control without established CVD or multiple CV risk factors with severe renal impairment.
- Patients on dialysis.

4.4. Special warnings and precautions for use

Dapagliflozin

Volume depletion

Before initiating, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy.

Insulin or Insulin Secretagogues:

The risk of hypoglycemia may be increased when dapagliflozin is used concomitantly with insulin or insulin secretagogues (e.g., sulfonylurea). Concomitant use may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.

Lithium:

Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more frequently during dapagliflozin initiation and dosage changes.

Ketoacidosis in Patients with Diabetes Mellitus

Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue medication, evaluate, and treat promptly. Before initiating, consider risk factors for ketoacidosis. Patients on dapagliflozin may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis.

Urosepsis and Pyelonephritis

Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Hypoglycemia

Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with drug.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene

Serious, life-threatening cases have occurred in patients with diabetes, both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment.

Genital Mycotic Infections

Monitor and treat if indicated.

Elderly (≥ 65 years)

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients.

Sacubitril/Valsartan

Fetal toxicity

Sacubitril and Valsartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, consider alternative drug treatment, and discontinue Sacubitril and Valsartan. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.

Angioedema

Sacubitril and Valsartan may cause angioedema. If angioedema occurs, discontinue Sacubitril and Valsartan immediately, provide appropriate therapy, and monitor for airway compromise. Sacubitril and Valsartan 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 edema may be fatal. Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, administer appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and take measures necessary to ensure maintenance of a patent airway.

Sacubitril and Valsartan has been associated with a higher rate of angioedema in Black than in non-black patients.

Patients with a prior history of angioedema may be at increased risk of angioedema with Sacubitril and Valsartan. Sacubitril and Valsartan must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. Sacubitril and Valsartan should not be used in patients with hereditary angioedema.

Hypotension

Sacubitril and Valsartan lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, such as volume-and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of Sacubitril and Valsartan or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage, or temporarily discontinue Sacubitril and Valsartan. Permanent discontinuation of therapy is usually not required.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with Sacubitril and Valsartan. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt Sacubitril and Valsartan in patients who develop a clinically significant decrease in renal function.

As with all drugs that affect the RAAS, Sacubitril and Valsartan may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.

Hyperkalemia

Through its actions on the RAAS, hyperkalemia may occur with Sacubitril and Valsartan. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of Sacubitril and Valsartan may be required.

4.5. Drugs interactions

Dapagliflozin

Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Carbonic Anhydrase Inhibitors

Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with Dapagliflozin and Metformin Hydrochloride Extended-Release Tablet may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

Drugs that Reduce Metformin Clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Dapagliflozin and Metformin Hydrochloride Extended-Release Tablet.

Sacubitril/Valsartan

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Concomitant use of Sacubitril and Valsartan with an ACE inhibitor is contraindicated because of the increased risk of angioedema.

Avoid use of Sacubitril and Valsartan with an ARB, because Sacubitril and Valsartan contains the angiotensin II receptor blocker valsartan.

The concomitant use of Sacubitril and Valsartan with aliskiren is contraindicated in patients with diabetes. Avoid use with aliskiren in patients with renal impairment (eGFR < 60 mL/min/1.73 m^2).

Potassium-Sparing Diuretics

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, with Sacubitril and Valsartan may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with Sacubitril and Valsartan.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Dapagliflozin

Patients with Renal impairment

Results of study, supported by results of population pharmacokinetic analyses, indicate that no dose adjustment is recommended in patients with renal impairment.

Hepatic Impairment

Patients with severe hepatic impairment (Child-Pugh class C) had comparable exposure of linagliptin in terms of AUC_{0-24} and approximately 23% lower Cmax compared with healthy subjects. Reductions in the pharmacokinetic parameters seen in patients with hepatic impairment did not result in reductions in DPP-4 inhibition.

Gender

No dose adjustment is necessary based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis.

Geriatric

No dose adjustment is recommended based on age, as age did not have a clinically meaningful impact on the pharmacokinetics of Dapagliflozin based on a population pharmacokinetic analysis.

Pediatric

Studies characterizing the pharmacokinetics of Dapagliflozin in pediatric patients have not yet been performed.

Pregnant Women

There are no data from the use of drug in pregnant women.

Lactating Women

It is unknown whether dapagliflozin (and/or its metabolites) are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically mediated effects in nursing offspring.

Sacubitril/Valsartan

Hepatic Impairment

No dose adjustment is required when administering Sacubitril and Valsartan to patients with mild hepatic impairment (Child-Pugh A classification). The recommended starting dose in

patients with moderate hepatic impairment (Child-Pugh B classification) is 24/26 mg twice daily. The use of Sacubitril and Valsartan in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended, as no studies have been conducted in these patients.

Renal Impairment

No dose adjustment is required in patients with mild (eGFR 60 to 90 mL/min/1.73 m2) to moderate (eGFR 30 to 60 mL/min/1.73 m2) renal impairment. The recommended starting dose in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) is 24/26 mg twice daily.

Pregnant Women

Sacubitril and Valsartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. In animal reproduction studies, Sacubitril and Valsartan treatment during organogenesis resulted in increased embryo-fetal lethality in rats and rabbits and teratogenicity in rabbits. When pregnancy is detected, consider alternative drug treatment, and discontinue Sacubitril and Valsartan. However, if there is no appropriate alternative to therapy with drugs affecting the renin angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.

Lactating Women

There is no information regarding the presence of Sacubitril and Valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sacubitril and Valsartan is present in rat milk. Because of the potential for serious adverse reactions in breastfed infants from exposure to Sacubitril and Valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with Sacubitril and Valsartan.

Paediatric Patients

The safety and effectiveness of Sacubitril and Valsartan in pediatric heart failure patients 1 to < 18 years old are supported by the reduction from baseline to 12 weeks in NT-proBNP in a randomized, double-blind clinical study. The analysis of NT-proBNP included 90 patients aged 6 to 18 years and 20 patients aged 1 to 6 years.

Safety and effectiveness have not been established in pediatric patients less than 1 year of age.

4.7. Effects on ability to drive and use machines

It has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Table: Adverse reactions in placebo-controlled clinical studies and postmarketing experience of Dapagliflozin

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections,	Fungal infection		Necrotising fasciitis of the perineum

System organ class	Very common	Common	Uncommon	Rare	Very rare
		Urinary tract infection			(Fournier's gangrene)
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)		Volume depletion, Thirst	Diabetic ketoacidosis (when used in type 2 diabetes mellitus)	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation, Dry mouth		
Skin and subcutaneous tissue disorders		Rash			Angioedema
Musculoskeletal and connective tissue disorders		Back pain			
Renal and urinary disorders		Dysuria Polyuria	Nocturia		Tubulointerstitial nephritis
Reproductive system and breast disorders		Vulvovaginal pruritus, Pruritus genital			
Investigations		Haematocrit, increased Creatinine, renal clearance decreased during initial treatment, Dyslipidaemia	Blood creatinine increased during initial treatment, Blood urea increased, Weight decreased		

Table: Adverse reactions in placebo-controlled clinical studies and post marketing experience of Sacubitril/Valsartan

System organ class	Very common	Common	Uncommon	Rare	Very rare
Cardiovascular	Hypotension	Orthostasis			

Metabolism and nutrition disorders	Hyperkalemia				
Renal and urinary disorders	Serum creatinine increased	Renal failure			
Respiratory system		Cough			
Nervous system		Dizziness			
Dermatologic			Angioedema		
Post marketing reports		Rash, Pruritus	Angioedema		

More common

- Hypotension
- Hyperkalaemia
- Cough
- Dizziness
- Abdominal or stomach pain
- Blurred vision
- Confusion
- Difficult breathing
- Faintness, or light-headedness when getting up suddenly from a lying or sitting position
- Irregular heartbeat
- Nausea or Vomiting
- Nervousness
- Numbness or tingling in the hands, feet, or lips.
- Sweating
- Unusual tiredness or weakness
- Weakness or heaviness of the legs

Less common

- Bloody urine
- Decreased frequency or amount of urine
- Increased thirst
- Loss of appetite
- Lower back or side pain

- Swelling of the face, fingers, or lower legs
- Weight gain

Rare

- Large, hive-like swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, or sex organs.

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose).

Limited data are available with regard to overdosage in human subjects with Sacubitril and Valsartan. In healthy volunteers, a single dose of 583 mg sacubitril/617 mg valsartan, and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) have been studied and were well tolerated. Hypotension is the most likely result of overdosage due to the blood pressure lowering effects of Sacubitril and Valsartan. Symptomatic treatment should be provided. Sacubitril and Valsartan is unlikely to be removed by hemodialysis because of high protein binding.

5. Pharmacological properties

5.1. Mechanism of Action

Dapagliflozin:

Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and diastolic function and preserve renal function. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF, DELIVER and DAPA-CKD studies. Other effects include an increase in haematocrit and reduction in body weight.

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose and/or low GFR, dapagliflozin has a low propensity to cause hypoglycaemia, as the amount of filtrated glucose is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin

secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.

The SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Sacubitril and Valsartan:

Sacubitril and Valsartan contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. Sacubitril and Valsartan inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT1) receptor via valsartan. The cardiovascular and renal effects of Sacubitril and Valsartan in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT1 receptor, and inhibits angiotensin II-dependent aldosterone release.

5.2. Pharmacodynamic properties

Dapagliflozin:

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2diabetes mellitus following the administration of dapagliflozin.

Sacubitril and Valsartan:

The pharmacodynamic effects of Sacubitril and 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 renin-angiotensin system blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of Sacubitril and Valsartan resulted in a significant non-sustained increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP compared to valsartan. In a 21-day study in HFrEF patients, Sacubitril and Valsartan significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1. Sacubitril and Valsartan also blocked the AT1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, Sacubitril and Valsartan decreased plasma NTproBNP (not a neprilysin substrate), and increased plasma BNP (a neprilysin substrate) and urine cGMP compared with enalapril.

In PARAMOUNT, a randomized, double-blind, 36-week study in patients with heart failure with LVEF ≥ 45% comparing 97/103 mg of Sacubitril and Valsartan (n=149) to 160 mg of valsartan (n =152) twice-daily, Sacubitril and Valsartan decreased NT-proBNP by 17% while valsartan increased NT-proBNP by 8% at Week 12 (p = 0.005).

5.3. Pharmacokinetic properties

Dapagliflozin

Absorption

Following oral administration of Dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in Dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of Dapagliflozin following the administration of a 10 mg dose is 78%. Administration of Dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and

prolongs T_{max} by approximately 1 hour but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and Dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of Dapagliflozin was 118 litres.

Metabolism

The metabolism of Dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield Dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-Oglucuronide accounted for 61% of a 50 mg [^{14}C]-Dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-Dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for Dapagliflozin is approximately 12.9 hours following a single oral dose of Dapagliflozin 10 mg.

Sacubitril and Valsartan

Absorption:

Following oral administration, sacubitril valsartan sodium hydrate dissociates into sacubitril, which is further metabolized to LBQ657, and valsartan, which 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 ≥ 60 % and 23 %, respectively.

Following twice daily dosing of sacubitril valsartan sodium hydrate, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates by 1,6-fold. Sacubitril valsartan sodium hydrate administration with food has no clinically significant impact on the systemic exposures of sacubitril, LBQ657 and valsartan. Although there is a decrease in exposure to valsartan when sacubitril valsartan sodium hydrate is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. Sacubitril valsartan sodium hydrate can therefore be administered with or without food.

Distribution:

Sacubitril valsartan sodium hydrate is highly bound to plasma proteins (94 % - 97 %). Based on the comparison of plasma and CSF exposures, LBQ657 does cross the blood brain barrier to a limited extent (0,28 %).

Metabolism

Sacubitril is readily converted to LBQ657 by esterases; 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 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.

Excretion

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 (T1/2) of approximately 1,43 hours, 11,48 hours, and 9,90 hours, respectively.

Clinical Studies

Dosing in clinical trials was based on the total amount of all components of Dapagliflozin and Sacubitril and Valsartan, i.e., 5/24/26 mg, 5/49/51 mg, and 5/97/103 mg were referred to as 5/50 mg, 5/100 mg, and 5/200 mg, respectively.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Dapagliflozin

In vivo primary pharmacodynamic studies with Dapagliflozin were carried out in single-dose, dose ranging studies in non-diabetic and diabetic rats or mice in order to evaluate the potency, SGLT2-specificity, and duration of action in stimulating urinary glucose excretion, and to describe the secondary consequences of urinary glucose excretion, such as changes in urine volume or blood or plasma glucose effects. Subsequently a multiple-dose study was carried out to evaluate the ability of Dapagliflozin to have sustained effects on urinary glucose excretion, urine volume, and fasting plasma glucose in diabetic rats over a two-week dosing period.

Dapagliflozin increased renal glucose excretion in (healthy, non-diabetic) experimental animals. This was accompanied, by osmotic diuresis as measured by increased urine flow. An oral glucose tolerance test was also performed showing that Dapagliflozin was able to significantly reduce glucose area under the curve (AUC), compared to vehicle treatment. A study in knock-out mice lacking the gene for SGLT2 revealed that SGLT2 is indeed the main target for Dapagliflozin at least at lower doses. This study also demonstrated the reversibility of Dapagliflozin's action towards SGLT2.

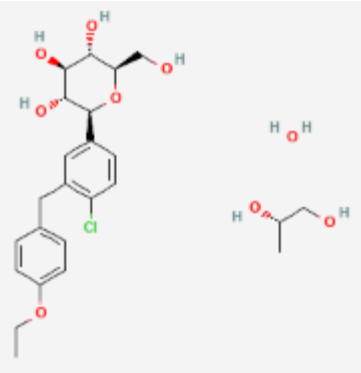
Sacubitril and Valsartan

The effects of Sacubitril and Valsartan on amyloid-β concentrations in CSF and brain tissue were assessed in young (2 to 4 years old) cynomolgus monkeys treated with Sacubitril and Valsartan (24 mg sacubitril/26 mg valsartan/kg/day) for 2 weeks. In this study, Sacubitril and Valsartan affected CSF Aβ clearance, increasing CSF Aβ 1-40, 1-42, and 1-38 levels in CSF; there was no corresponding increase in Aβ levels in the brain. In addition, in a toxicology study in cynomolgus monkeys treated with Sacubitril and Valsartan at 146 mg sacubitril/154 mg valsartan/kg/day for 39-weeks, there was no amyloid-β accumulation in the brain.

7. Description

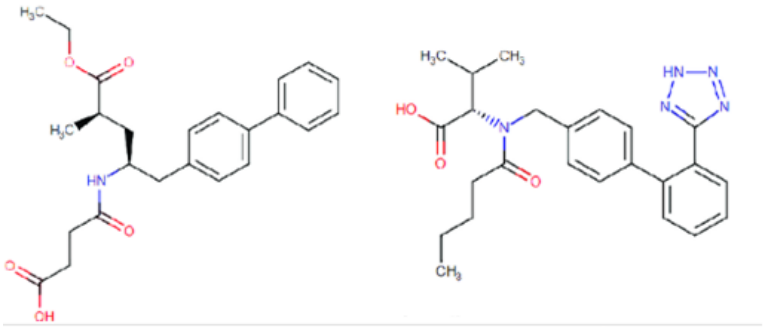
Dapagliflozin:

Dapagliflozin Propanediol is (2S,3R,4R,5S,6R)-2-(4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl)-6-(hydroxymethyl) oxane-3,4,5-triol; (2S)-propane-1,2-diol. The empirical formula is $C_{21}H_{25}ClO_6 . C_3H_8O_2 . H_2O$ and its molecular weight is 502.98 g/mol. The chemical structural formula is:



Sacubitril Valsartan Complex:

Sacubitril Valsartan is 4-[[(2S,4R)-5-ethoxy-4-methyl-5-oxo-1-(4-phenylphenyl) pentan-2-yl] amino]-4-oxobutanoic acid;(2S)-3-methyl-2-[pentanoyl-[[4-[2-(2H-tetrazol-5-yl) phenyl] phenyl] methyl] amino] butanoic acid. The empirical formula is $C_{48}H_{55}N_6Na_3O_8$. $2.5H_2O$ and its molecular weight is 915.98 g/mol. The chemical structural formula is:



ARNOZA D (5+50)

Dapagliflozin and Sacubitril Valsartan Tablets is Light pink colored, Almond shape, biconvex, film coated tablets, plain on both sides. The excipients used are Colloidal Silicon dioxide, Microcrystalline Cellulose, Povidone K-30, Isopropyl Alcohol, Microcrystalline Cellulose, Crospovidone, Colloidal Silicon Dioxide, Purified Talc, Calcium Stearate, Hydroxy propyl methyl cellulose, Polyethylene Glycol, Titanium Dioxide, Ferric Oxide Red, Ferroso Ferric Oxide USP.

ARNOZA D (5+100)

Dapagliflozin and Sacubitril Valsartan Tablets is Yellow colored, capsule shape, biconvex, film coated tablets, plain on both sides. The excipients used are Colloidal Silicon dioxide, Microcrystalline Cellulose, Povidone K-30, Isopropyl Alcohol, Microcrystalline Cellulose, Crospovidone, Colloidal Silicon Dioxide, Purified Talc, Calcium Stearate, Hydroxy propyl methyl cellulose, Polyethylene Glycol, Talc, Titanium Dioxide, Ferric Oxide Red, Ferric Oxide Yellow.

ARNOZA D (5+200)

Dapagliflozin and Sacubitril Valsartan Tablets is Reddish Brown colored, oval shape, biconvex, film coated tablets, plain on both sides. The excipients used are Colloidal Silicon dioxide, Microcrystalline Cellulose, Povidone K-30, Isopropyl Alcohol, Microcrystalline Cellulose, Crospovidone, Colloidal Silicon Dioxide, Purified Talc, Calcium Stearate, Titanium Dioxide, Red Iron Oxide.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

ARNOZA D is available in Alu-Alu Blister Pack of 10 Tablets.

8.4. Storage and handing instructions

Store below 30°C.

Keep all medicines out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Exemed Pharmaceuticals,

Plot No. 133/1 & 133/2,

GLDC Selvas Road,

Vapi, Dist: - Valsad – 396 195, Gujarat State, India.

11. Details of permission or licence number with date

Mfg. Licence No.: G/25/2011 Issued on 27 Oct 2025.

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ARNOZA D (5mg + 50mg/5mg + 100mg/5mg + 200mg)/JAN-2026/01/PI