Front

FORHEF™

[Sacubitril + Valsartan]

TABLET

فارہیف

COMPOSITION:
FORHEF 24 mg/26 mg Tablet:
Each film coated tablet contains:
Sacubitril ..... 24 mg.
Valsartan ..... 26 mg.

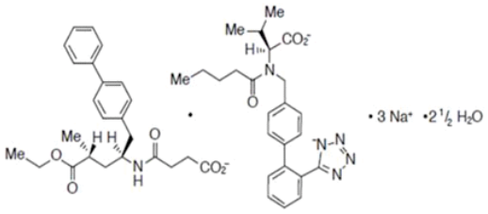
Product Specs.: Innovator

FORHEF 49 mg/51 mg Tablet:
Each film coated tablet contains:
Sacubitril ..... 49 mg.
Valsartan ..... 51 mg.

Product Specs.: Innovator

WARNING: FETAL TOXICITY
See full prescribing information for complete boxed warning.
- When pregnancy is detected, discontinue FORHEF as soon as possible.
- Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

DESCRIPTION:
SACUBITRIL/VALSARTAN is a combination of a neprilysin inhibitor and an angiotensin II receptor blocker. It contains a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex is chemically described as. Octadecasodiumhexakis(4-{[(1S,3R)-1-{[1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4¬ oxobutanoate)hexakis(N-pentanoyl-N-{[2´-(1H-tetrazol-1-id-5-yl)[1,1´-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15). Its empirical formula (hemipentahydrate) is $C_{48}H_{55}N_6O_8Na3$ 2.5 H_2O. Its molecular mass is 957.99 and its schematic structural formula is:



Mechanism of Action:
SACUBITRIL/VALSARTAN contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. It 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/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 also inhibits angiotensin II-dependent aldosterone release.

CLINICAL PHARMACOLOGY:
Pharmacokinetics: Sacubitril; valsartan is administered orally. Sacubitril and valsartan are highly bound to plasma proteins (more than 94%). Sacubitril is converted to its active metabolite, LBQ657, by plasma esterases and not further metabolized. Valsartan is minimally metabolized; approximately 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified at low concentrations (less than 10%) in plasma. LBQ657 crosses the blood brain barrier to a minimal extent (0.28%). The average volume of distribution of sacubitril and valsartan are 103 and 75 L, respectively. After oral administration, 52% to 68% of sacubitril (primarily as metabolite) and approximately 13% of valsartan and its metabolites are excreted in urine. The remaining drug and metabolites are excreted in feces. Sacubitril, LBQ657, and valsartan exhibit a mean elimination half-life of approximately 1.4, 11.5, and 9.9 hours, respectively.

In a 21-day study of patients with heart failure and reduced ejection fraction, sacubitril; valsartan administration resulted in significantly increased urine atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP) and plasma cGMP, and decreased plasma N-terminal pro b-type natriuretic peptide (NT-proBNP), aldosterone, and endothelin-1. Sacubitril; valsartan blocked the AT1-receptor resulting in increased plasma renin activity and plasma renin concentrations.

Affected cytochrome P450 isoenzymes and drug transporters: CYP2C9, OATP1B1, OATP1B3, MRP2 Valsartan does not inhibit CYP450 isoenzymes at clinically relevant concentrations. In vitro studies indicate CYP2C9 is the isoenzyme responsible for the formation of valeryl-4-hydroxy valsartan. An in vitro study with human liver tissue indicates that it is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. In vitro data also indicate that sacubitril inhibits OATP1B1 and OSTP1B3 transporters.
Pharmacodynamics: 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 renin-angiotensin system blockade. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of SACUBITRIL/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/VALSARTAN significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1. SACUBITRIL/VALSARTAN also blocked the AT1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, SACUBITRIL/VALSARTAN decreased plasma NTproBNP (not a neprilysin substrate) and increased plasma BNP (a neprilysin substrate) and urine cGMP compared with enalapril. QT Prolongation: 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 repolarization.
Amyloid-β: 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 2 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 or CSF Aβ1-42. The clinical relevance of this finding is unknown. Blood ***Pressure***: Addition of a 50 mg single dose of sildenafil to SACUBITRIL/VALSARTAN at steady state (194 mg sacubitril/206 mg valsartan once daily for 5 days) in patients with hypertension was associated with additional blood pressure (BP) reduction (~ 5/4 mmHg, systolic/diastolic BP) compared to administration of SACUBITRIL/VALSARTAN alone. Co-administration of SACUBITRIL/VALSARTAN did not significantly alter the BP effect of intravenous nitroglycerin.

INDICATIONS:
Adult heart failure: SACUBITRIL/VALSARTAN is indicated 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. SACUBITRIL/VALSARTAN is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.
Pediatric heart failure: SACUBITRIL/VALSARTAN is indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. SACUBITRIL/VALSARTAN reduces NT-proBNP and is expected to improve cardiovascular outcomes.

DOSAGE AND ADMINISTRATION:
General considerations: SACUBITRIL/VALSARTAN is contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. If switching from an ACE inhibitor to SACUBITRIL/VALSARTAN allow a washout period of 36 hours between administration of the two drugs.

ADULTS:
Adults NOT currently taking an ACE inhibitor or ARB
24 mg sacubitril; 26 mg valsartan PO twice daily initially. Double the dose every 2 to 4 weeks as tolerated to the target maintenance dose of 97 mg sacubitril; 103 mg valsartan PO twice daily. Guidelines recommend an angiotensin receptor-neprilysin inhibitor (ARNI) and ARB in combination with an evidence-based beta blocker and aldosterone antagonist, in select patients, for patients with chronic reduced ejection fraction heart failure (HFrEF) NYHA class II or III to reduce morbidity and mortality. In patients with chronic symptomatic HFrEF class II or III who tolerate an ACE inhibitor or ARB, replacement by ARNI therapy is recommended.
Adults previously taking low dose ACE inhibitor or ARB
24 mg sacubitril; 26 mg valsartan PO twice daily initially. Double the dose every 2 to 4 weeks as tolerated to the target maintenance dose of 97 mg sacubitril; 103 mg valsartan PO twice daily. Guidelines recommend an angiotensin receptor-neprilysin inhibitor (ARNI) and ARB in combination with an evidence-based beta blocker and aldosterone antagonist, in select patients, for patients with chronic reduced ejection fraction heart failure (HFrEF) NYHA class II or III to reduce morbidity and mortality. In patients with chronic symptomatic HFrEF class II or III who tolerate an ACE inhibitor or ARB, replacement by ARNI therapy is recommended.
Adults previously taking moderate to high dose ACE inhibitor or ARB
49 mg sacubitril; 51 mg valsartan PO twice daily initially. After 2 to 4 weeks, increase the dose to the target maintenance dose of 97 mg sacubitril; 103 mg valsartan PO twice daily as tolerated. Guidelines recommend an angiotensin receptor-neprilysin inhibitor (ARNI) and ARB in combination with an evidence-based beta blocker and aldosterone antagonist, in select patients, for patients with chronic reduced ejection fraction heart failure (HFrEF) NYHA class II or III to reduce morbidity and mortality. In patients with chronic symptomatic HFrEF class II or III who tolerate an ACE inhibitor or ARB, replacement by ARNI therapy is recommended.

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PEDIATRIC:
Children and Adolescents weighing 50 kg or more NOT currently taking an ACE inhibitor or ARB
24 mg sacubitril; 26 mg valsartan PO twice daily initially. Titrate every 2 weeks as tolerated, first to 49 mg sacubitril; 51 mg valsartan PO twice daily, next to 72 mg sacubitril; 78 mg valsartan PO twice daily, then to 97 mg sacubitril; 103 mg valsartan PO twice daily.
Children and Adolescents weighing 50 kg or more previously taking low dose ACE inhibitor or ARB
24 mg sacubitril; 26 mg valsartan PO twice daily initially. Titrate every 2 weeks as tolerated, first to 49 mg sacubitril; 51 mg valsartan PO twice daily, next to 72 mg sacubitril; 78 mg valsartan PO twice daily, then to 97 mg sacubitril; 103 mg valsartan PO twice daily.
Children and Adolescents weighing 50 kg or more previously taking moderate to high dose ACE inhibitor or ARB
49 mg sacubitril; 51 mg valsartan PO twice daily initially. Titrate every 2 weeks as tolerated, first to 72 mg sacubitril; 78 mg valsartan PO twice daily, then to 97 mg sacubitril; 103 mg valsartan PO twice daily.
Children and Adolescents weighing 40 to 49 kg NOT currently taking an ACE inhibitor or ARB
0.8 mg/kg/dose (combined amount of sacubitril and valsartan) PO twice daily initially. Titrate every 2 weeks as tolerated, first to 24 mg sacubitril; 26 mg valsartan PO twice daily, next to 49 mg sacubitril; 51 mg valsartan PO twice daily, then to 72 sacubitril; 78 mg valsartan PO twice daily.
Children and Adolescents weighing 40 to 49 kg previously taking low dose ACE inhibitor or ARB
0.8 mg/kg/dose (combined amount of sacubitril and valsartan) PO twice daily initially. Titrate every 2 weeks as tolerated, first to 24 mg sacubitril; 26 mg valsartan PO twice daily, next to 49 mg sacubitril; 51 mg valsartan PO twice daily, then to 72 sacubitril; 78 mg valsartan PO twice daily.
Children and Adolescents weighing 40 to 49 kg previously taking moderate to high dose ACE inhibitor or ARB
24 mg sacubitril; 26 mg valsartan PO twice daily initially. Titrate every 2 weeks as tolerated, first to 49 mg sacubitril; 51 mg valsartan PO twice daily, then to 72 mg sacubitril; 78 mg valsartan PO twice daily.
Children and Adolescents weighing less than 40 kg NOT currently taking an ACE inhibitor or ARB
0.8 mg/kg/dose (combined amount of sacubitril and valsartan) PO twice daily initially. Titrate every 2 weeks as tolerated, first to 1.6 mg/kg/dose PO twice daily, next to 2.3 mg/kg/dose PO twice daily, then to 3.1 mg/kg/dose PO twice daily.
Children and Adolescents weighing less than 40 kg previously taking moderate to high dose ACE inhibitor or ARB
1.6 mg/kg/dose (combined amount of sacubitril and valsartan) PO twice daily initially. Titrate every 2 weeks as tolerated, first to 2.3 mg/kg/dose PO twice daily, then to 3.1 mg/kg/dose PO twice daily.

WARNINGS & PRECAUTIONS:
Fetal toxicity: SACUBITRIL/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/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/VALSARTAN may cause angioedema. In the double-blind period of PARADIGM-HF, 0.5% of patients treated with SACUBITRIL/VALSARTAN and 0.2% of patients treated with enalapril had. If angioedema occurs, discontinue SACUBITRIL/VALSARTAN immediately, provide appropriate therapy, and monitor for airway compromise. SACUBITRIL/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/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/VALSARTAN. SACUBITRIL/VALSARTAN must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. SACUBITRIL/VALSARTAN should not be used in patients with hereditary angioedema.
Hypotension: SACUBITRIL/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. In the double-blind period of PARADIGM-HF, 18% of patients treated with SACUBITRIL/VALSARTAN and 12% of patients treated with enalapril reported hypotension as an adverse event with hypotension reported as a serious adverse event in approximately 1.5% of patients in both treatment arms. Correct volume or salt depletion prior to administration of SACUBITRIL/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/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/VALSARTAN. In the double-blind period of PARADIGM-HF, 5% of patients in both the SACUBITRIL/VALSARTAN and enalapril groups reported renal failure as an adverse event. 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/VALSARTAN in patients who develop a clinically significant decrease in renal function. As with all drugs that affect the RAAS, SACUBITRIL/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/VALSARTAN. In the double-blind period of PARADIGM-HF, 12% of patients treated with SACUBITRIL/VALSARTAN and 14% of patients treated with enalapril reported hyperkalemia as an adverse event. 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/VALSARTAN may be required.

ADVERSE REACTIONS: See Warnings and Precautions.

SPECIAL POPULATIONS:
Pregnancy: SACUBITRIL/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. When pregnancy is detected, consider alternative drug treatment and discontinue SACUBITRIL/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. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
Clinical considerations: Fetal/Neonatal Adverse Reactions Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of in utero exposure to SACUBITRIL/VALSARTAN for hypotension, oliguria, and hyperkalemia. In neonates with a history of in utero exposure to SACUBITRIL/VALSARTAN, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.
Lactation: Risk Summary There is no information regarding the presence of sacubitril/valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sacubitril/valsartan is present in rat milk. Because of the potential for serious adverse reactions in breastfed infants from exposure to sacubitril/valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with SACUBITRIL/VALSARTAN.
Geriatric use: No relevant pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population.
Hepatic impairment: See Dosage & Administration.
Renal impairment: See Dosage & Administration.

CONTRAINDICATIONS:
SACUBITRIL/VALSARTAN is contraindicated:
- In patients with hypersensitivity to any component
- 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.

DRUG INTERACTIONS:
Dual blockade of the Renin-Angiotensin-Aldosterone system: Concomitant use of SACUBITRIL/VALSARTAN with an ACE inhibitor is contraindicated because of the increased risk of angioedema. Avoid use of SACUBITRIL/VALSARTAN with an ARB, because SACUBITRIL/VALSARTAN contains the angiotensin II receptor blocker valsartan. The concomitant use of SACUBITRIL/VALSARTAN with aliskiren is contraindicated in patients with diabetes. Avoid use with aliskiren in patients with renal impairment (eGFR < 60 mL/min/1.73 m²).
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/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/VALSARTAN.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight and moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

PRESENTATION:

FORHEF 24 mg/26 mg Tablet	:	Pack of 2 x 7 tablets.
FORHEF 49 mg/51 mg Tablet	:	Pack of 2 x 7 tablets.

FOR FURTHER INFORMATIONS PLEASE CONTACT:

Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
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