Sacvin®

(Sacubitril/Valsartan)

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COMPOSITION

SACVIN 50
Sacubitril.....24mg
Valsartan.....26mg
(as Sacubitril Valsartan sodium salt complex)
SACVIN 100
Sacubitril.....49mg
Valsartan.....51mg
(as Sacubitril Valsartan sodium salt complex)
SACVIN 200
Sacubitril.....97mg
Valsartan.....103mg
(as Sacubitril Valsartan sodium salt complex)
(As Per Innovator's Specs.)

WARNING: PREGNANCY AND FETAL TOXICITY
Drugs that act directly on the renin-angiotensin system such as Valsartan can cause injury and death to the developing fetus. When pregnancy is detected, Valsartan should be discontinued as soon as possible.

DESCRIPTION

SACVIN is a combination of a neprilysin inhibitor, sacubitril and an angiotensin II receptor blocker, 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. Its molecular formula is $C_{48}H_{55}N_6O_8Na_{32.5}H_2O$

CLINICAL PHARMACOLOGY

Mechanism of Action
SACVIN contains a neprilysin inhibitor, Sacubitril, and an angiotensin receptor blocker, Valsartan. Sacubitril inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and Valsartan blocks the angiotensin II type-1 (AT1) receptor.

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 (NPs), 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 the 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 remodelling

Pharmacodynamics:
The pharmacodynamic effects of Sacubitril/Valsartan are consistent with simultaneous neprilysin inhibition and RAAS blockade after single and multiple dose administrations in healthy patients and in patients with heart failure. In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of Sacubitri/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 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 AT1-receptor was also blocked as evidenced by increased plasma renin activity and plasma renin concentrations. In the PARADIGM-HF study, Sacubitri/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. NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.
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.

Pharmacokinetics

Absorption
Following oral administration, the combination tablet dissociates into sacubitril and valsartan. Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be ≥ 60%. Following twice-daily dosing of the combination tablet Sacubitril/Valsartan, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days. Administration with food has no clinically significant effect on the systemic exposures of sacubitril, LBQ657, or valsartan. Sacubitril/Valsartan tablet can therefore 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 are 75 to 103 L, respectively.

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

Excretion
Following oral administration, 52-68% of sacubitril (primarily as LBQ657) and nearly 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 feces. Sacubitril, LBQ657 and valsartan are eliminated from plasma with a mean elimination half-life (T½) of approximately 1.43 hours, 11.48 hours, and 9.90 hours, respectively.

INDICATIONS

Heart Failure
SACVIN (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.

SACVIN (Sacubitril/Valsartan) is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

DOSAGE AND ADMINISTRATION

The recommended starting dose of SACVIN is one 49/51 mg (sacubitril/valsartan) tablet twice-daily.

Double the dose of SACVIN after 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient.

Reduce the starting dose to 24/26 mg (sacubitril/valsartan) twice-daily for:
• Patients not currently taking an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) or previously taking a low dose of these agents.
• Patients with severe renal impairment (CrCl less than 30 ml/min)
• Patients with moderate hepatic impairment. (Child Pugh B)

Double the dose of SACVIN every 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient.

Dose adjustment in special populations

Renal Impairment
A starting dose of 24/26 mg twice-daily is recommended for patients with severe renal impairment (creatinine clearance <30 mL/min). Double the dose of SACVIN every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient. No starting dose adjustment is needed for mild or moderate renal impairment. There is no experience in patients with end-stage renal disease and use of Sacubitril/Valsartan is not recommended.

Hepatic Impairment
A starting dose of 24/26 mg twice-daily is recommended for patients with moderate hepatic impairment (Child-Pugh B classification) or in patients with AST/ALT values more than twice the upper limit of the normal range. Double the dose of SACVIN every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient. No starting dose adjustment is needed for mild hepatic impairment.

Use in patients with severe hepatic impairment, biliary cirrhosis or cholestasis is not recommended.

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

Administration requirements
SACVIN may be administered with or without food. The tablets must be swallowed with a glass of water.

CONTRAINDICATIONS

• Hypersensitivity to Valsartan and Sacubitril.
• Concomitant use with ACE inhibitors. SACVIN must not be administered within 36 hours of switching from or to an ACE inhibitor.
• Known history of angioedema related to previous ACE inhibitor or ARB therapy.
• Hereditary or idiopathic angioedema.
• Concomitant use with aliskiren-containing products in patients with diabetes mellitus or in patients with renal impairment (creatinine clearance <60 ml/min).
• Severe hepatic impairment, biliary cirrhosis and cholestasis.
• Second and third trimester of pregnancy.

WARNINGS AND 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. See USE IN SPECIAL POPULATIONS

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. 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.

A starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg. Treatment should not be initiated in patients with SBP <100 mmHg

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
The combination of Sacubitril /Valsartan with an ACE inhibitor is contraindicated due to the increased risk of angioedema. Sacubitril /Valsartan must not be used within 36 hours of switching from or to an ACE inhibitor. The combination of Sacubitril /Valsartan with direct renin inhibitors such as aliskiren is not recommended. The combination of Sacubitril /Valsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or in patients with renal impairment (CrCl <60 ml/min).
SACVIN contains valsartan, and therefore should not be co-administered with another ARB containing product.

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. Patients with severe renal impairment (estimated CrCl <30 ml/min) may be at greatest risk of hypotension and a starting dose of 24/26 mg twice-daily is recommended. There is no experience in patients with end-stage renal disease and use of Sacubitril/Valsartan is not recommended in these patients

Worsening renal function
Due to inhibition of the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with Sacubitril/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 angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. The risk may be further increased by dehydration or concomitant use of non-steroidal anti-inflammatory agents (NSAIDs). Down-titration or discontinuation should be considered in patients who develop a clinically significant decrease in renal function. Monitor serum creatinine closely in such patients

Impaired hepatic function
There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range. In these patients, exposure may be increased and safety is not established. Caution is therefore recommended when using it in these patients with a recommended starting dose of 24/26 mg twice-daily. Sacubitril/Valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification).

Hyperkalemia
Treatment should not be initiated with Sacubitril/Valsartan, if the serum potassium level is >5.4

mmol/L. Use of Sacubitril/Valsartan may be associated with an increased risk of hyperkalaemia, although hypokalemia may also occur. 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. If patients experience clinically significant hyperkalemia adjustment of concomitant drugs, 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, product should be immediately discontinued and appropriate therapy and monitoring should be provided. 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 may be at higher risk for angioedema, caution is recommended if Sacubitril/Valsartan is used in these patients. Sacubitril/Valsartan is contraindicated in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy or with hereditary or idiopathic angioedema. Black patients have an increased susceptibility to develop angioedema.

Patients with renal artery stenosis
Sacubitril/Valsartan may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. Caution is required in patients with renal artery stenosis and monitoring of renal function is recommended.

Patients with NYHA functional classification IV
Caution should be exercised when initiating Sacubitril/Valsartan 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 Sacubitril/Valsartan because it is a neprilysin substrate.

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

ADVERSE REACTIONS

Blood and lymphatic system disorders
Common: Anemia
Immune system disorders
Uncommon: Hypersensitivity
Metabolism and nutrition disorders
Very common: Hyperkalemia
Common: Hypokalemia, Hypoglycemia
Nervous system disorders
Common: Dizziness, Headache, Syncope
Uncommon: Dizziness postural
Ear and labyrinth disorders
Common: Vertigo
Vascular disorders
Very common: Hypotension
Common: Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Common: Cough
Gastrointestinal disorders
Common: Diarrhea, Nausea, Gastritis
Skin and subcutaneous tissue disorders
Uncommon: Pruritus, Rash, Angioedema
Renal and urinary disorders
Very common: Renal impairment
Common: Renal failure (renal failure, acute renal failure)
General disorders and administration site conditions
Common: Fatigue, Asthenia

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 SACVIN with an ARB, because SACVIN contains the angiotensin II receptor blocker valsartan. The concomitant use of Sacubitril/Valsartan with aliskiren is not recommended and contraindicated in patients with diabetes and in patients with renal impairment (creatinine clearance <60 mL/min). Combination of Sacubitril/Valsartan with aliskiren is potentially associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure)

Drugs causing hyperkalemia
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 or other agents (such as heparin) may lead to increases in serum potassium when used concomitantly with Sacubitril/Valsartan [see Warnings and Precautions].

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.

OATP1B1 and OATP1B3 substrates (statins)

Sacubitril inhibits OATP1B1 and OATP1B3 transporters. Sacubitril/Valsartan may therefore increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. Caution should be exercised when co-administering Sacubitril/Valsartan with statins.

PDE5 inhibitors including sildenafil

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

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/Valsartan with inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampicin, cyclosporine), OAT1 (e.g. tenofovir, cidofovir) or MRP2 (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 drugs.

USE IN SPECIAL POPULATIONS

Pregnancy

Sacubitril/Valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy.

Valsartan
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. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ARBs should be stopped immediately and, if appropriate, alternative therapy should be started. Exposure to ARBs therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

Should exposure to ARBs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. 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.

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

Nursing mothers
It is not known whether Sacubitril/Valsartan is excreted in human milk. Because of the potential risk for adverse reactions in breast-fed newborns/infants, it is not recommended during breast-feeding. A decision should be made whether to abstain from breast-feeding or to discontinue SACVIN while breast-feeding, taking into account the importance of the drug to the mother.
Pediatrics
Safety and effectiveness in pediatric patients have not been established.

Elderly (age 65 years or over)
No relevant pharmacokinetic differences have been observed in elderly (≥65 years) or very elderly (≥75 years) patients compared to the overall population.

Renal impairment
The exposure of LBQ657, active metabolite of Sacubitril in patients with moderate (30 ml/min ≤ CrCl <60 ml/min) and severe renal impairment (15 ml/min ≤ CrCl <30 ml/min) was 1.4-fold and 2.2-fold higher compared to patients with mild renal impairment (60 ml/min ≤ CrCl <90 ml/min). The exposure of valsartan was similar in patients with moderate and severe renal impairment compared to patients with mild renal impairment. No data exists for patients undergoing dialysis. However, LBQ657 and valsartan are highly bound to plasma protein and therefore unlikely to be effectively removed by dialysis.

No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min/) to moderate (CrCl 30 to 60 mL/min) renal impairment. The recommended starting dose in patients with severe renal impairment (CrCl <30 mL/min) is 24/26 mg twice daily. There is no experience in patients with ESRD (End-Stage-Renal-Disease) and use of Sacubitril/Valsartan is not recommended in ESRD.

Hepatic impairment
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 dose adjustment is required when administering SACVIN 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 SACVIN in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended, as no studies have been conducted in these patients.

OVER DOSAGE
Limited data are available with regard to overdose in humans. A single dose of 583 mg sacubitril/617 mg valsartan and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) were studied in healthy volunteers and were well tolerated.

Symptoms
Hypotension is the most likely symptom of overdose due to the blood pressure lowering effects of Sacubitril/Valsartan.

Treatment
Symptomatic treatment should be provided in case of overdose. Sacubitril/Valsartan is unlikely to be removed by hemodialysis due to high protein binding.

PRESENTATION

SACVIN 50
Available in the pack of 30's tablets.
SACVIN 100
Available in the pack of 30's tablets.
SACVIN 200
Available in the pack of 30's tablets.

INSTRUCTIONS

Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, report at pharmacovigilance@pharmevo.biz

For more information on our products call PharmAssist helpline 0800-82222 Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz

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