Sacuvia™

(Sacubitril + Valsartan)

Highnoon

COMPOSITION

Sacuvia 50mg Tablet: Each film-coated tablet contains:
Sacubitril 24mg
Valsartan 26mg
(as Sodium Salt Complex)

Sacuvia 100mg Tablet: Each film-coated tablet contains:
Sacubitril 49mg
Valsartan 51mg
(as Sodium Salt Complex)

Sacuvia 200mg Tablet: Each film-coated tablet contains:
Sacubitril 97mg
Valsartan 103mg
(as Sodium Salt Complex)

DESCRIPTION

SACUVIA (sacubitril and valsartan) is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker.

MECHANISM OF ACTION

SACUVIA (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 and valsartan combination 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.

PHARMACOKINETICS

Valsartan

Valsartan is rapidly absorbed after oral doses, with a bioavailability of about 23% when given as a tablet and about 39% when given as a solution. Peak plasma concentrations of valsartan occur 2 to 4 hours after tablet and 1 to 2 hours after oral solution. It is between 94 and 97% bound to plasma proteins. Valsartan is not significantly metabolized and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 6 hours. Following an oral dose, about 83% excreted in the faeces, and 13% in urine.

Sacubitril

Sacubitril is metabolized to LBQ657. The peak plasma concentrations of sacubitril, (LBQ657), reached in 0.5 and 2 hours. The absolute oral bioavailability of sacubitril is estimated to be ≥ 60%. LBQ657 is highly bound to plasma proteins (94%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Following oral administration, 52% to 68% of sacubitril, primarily as LBQ657, excreted in urine and 37% to 48% of sacubitril, primarily as LBQ657, excreted in feces. Sacubitril & LBQ657 eliminated from plasma with a mean elimination half-life (T1/2) of approximately 1.4 hours and 11.5 hours respectively. It can therefore be administered with or without food.

INDICATIONS AND USAGE

- It is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.
- It is indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. It reduces NT-proBNP and is expected to improve cardiovascular outcomes.

DOSAGE AND ADMINISTRATION

- The recommended starting dose of SACUVIA (sacubitril and valsartan) is 49mg/51mg, twice-daily. Double the dose of SACUVIA (sacubitril and valsartan) after 2 to 4 weeks to the target maintenance dose of 97mg/103mg, twice daily, as tolerated by the patient.
- For pediatric patient aged one year and older, the recommended dose is twice daily orally. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient:

Recommended dose titration.

Pediatrics Patient	Titration step dose (twice daily)		
	Starting	Second	Final
Weight less than 40 kg	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Weight at least 40 kg, less than 50 kg	24mg/26mg	49mg/51mg	72mg/78mg
Weight at least 50kg	49mg/51mg	72mg/78mg	97mg/103mg

Dose adjustment for patients not taking an ACE inhibitor or ARB or previously taking low doses of these agents

A starting dose of 24mg/26mg twice-daily is recommended for patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients to follow the recommended dose escalation thereafter. Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily.

Dose adjustment for severe renal impairment

A starting dose of 24mg/26mg twice-daily is recommended for patients with severe renal impairment (eGFR <30 mL/min/1.73 m²). After initiation, increase the dose to follow the recommended dose escalation thereafter. Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily. No starting dose adjustment is needed for mild or moderate renal impairment.

Dose adjustment for hepatic impairment

A starting dose of 24mg/26mg twice-daily is recommended for patients with moderate hepatic impairment (Child-Pugh B classification). After initiation, increase the dose to follow the recommended dose escalation thereafter.
Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily. No starting dose adjustment is needed for mild hepatic impairment. It is not recommended in severe hepatic impairment.

CONTRAINDICATIONS

It 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.

WARNINGS AND PRECAUTIONS

- When administered to a pregnant woman this medicine (sacubitril and valsartan) can cause fetal harm. 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 it. 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.
- It 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 it or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs treat other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue it. Permanent discontinuation of therapy is usually not required.
- Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend, in part, on the activity of the renin-angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Periodically monitor renal function (serum creatinine) in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Valsartan.
- Some patients with heart failure have developed increases in potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. 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 and/or discontinuation of it may be required.
- It may cause angioedema. If angioedema occurs, discontinue it immediately, provide appropriate therapy, and monitor for airway compromise. It must not be re-administered, in cases of confirmed angioedema, where swelling has been confined to the face and lips, and condition had generally resolved without treatment. Antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where the involvement of the tongue, glottis or larynx is likely to cause airway obstruction, administer appropriate therapy and take necessary measures to ensure maintenance of a patent airway. It must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy. It should not be used in patients with hereditary angioedema.

ADVERSE REACTIONS:

The reported adverse events are angioedema, hyperkalemia, hypotension, orthostatic hypotension, impaired renal function, cough, dizziness, acute renal failure, orthostasis, falls, decrease in hemoglobin and hematocrit, elevations in serum creatinine, elevations in serum potassium, hypersensitivity including rash, pruritus and anaphylactic reaction.
Other reported adverse reactions are anemia, headache, syncope, vertigo, cough, diarrhoea, nausea, gastritis, fatigue, asthenia, auditory and visual hallucinations, sleep disorders, paranoia.

DRUG INTERACTIONS

- Valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Coadministration of inhibitors of the uptake transporter(rifampin ,cyclosporine),or efflux transporter (ritonavir)may increase the systemic exposure to valsartan. Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels. If co-medication is considered necessary, monitoring of serum potassium is advisable.
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy.
- Dual blockade of the Renin Angiotensin System; it's concomitant use with ACE inhibitors is contraindicated because of increased risk of angioedema. Avoid its use with angiotensin receptor blockers because it contains the angiotensin II receptor blocker valsartan. Its concomitant use with aliskiren is contraindicated in patient with diabetes and avoid use with aliskiren in patients with renal impairment (eGFR <60 mL/min/1.73 m²).
- Do not coadminister aliskiren with Valsartan in patients with diabetes. Avoid use of aliskiren with Valsartan in patients with renal impairment (eGFR <60 mL/min/1.73 m²).
- 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 .
- Elevations in creatinine, decrease in hemoglobin & hematocrit, occasional elevation of liver chemistries, neutropenia, increase in serum potassium and blood urea nitrogen was observed in patients taking Valsartan. Proper monitoring and caution should be taken while using Valsartan.
- 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.
- Co-administration of sacubitril/valsartan and furosemide had no effect on the pharmacokinetics of sacubitril/valsartan but reduced Cmax and AUC of furosemide by 50% and 28%, respectively.
- 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, ciclosporin), 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 medicinal products.
- Co-administration of sacubitril/valsartan with metformin reduced both Cmax and AUC of metformin by 23%. Therefore, when initiating therapy with sacubitril/valsartan in patients receiving metformin, the clinical status of the patient should be evaluated.
- No clinically meaningful drug-drug interaction was observed when sacubitril/valsartan was co-administered with digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol or a combination of levonorgestrel/ethinyl estradiol.

USE IN SPECIFIC POPULATIONS

Pregnancy

The use of sacubitril/valsartan is not recommended during the first trimester of pregnancy and is contraindicated during the second and third trimesters of pregnancy 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. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue valsartan as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.
When there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system and if the drug is considered life saving for the mother, advise a pregnant women of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue valsartan, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to valsartan for hypotension, oliguria, and hyperkalemia.

Nursing Mothers

It is not known whether sacubitril and valsartan is excreted in human milk. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from exposure to sacubitril and valsartan, advise nursing women that breastfeeding is not recommended during treatment with sacubitril and valsartan combination.

Pediatric Use

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

Geriatric Use

There were no notable differences in efficacy or safety between older and younger patients.

Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh A classification). The recommended starting dose in patient with moderate hepatic impairment (Child-Pugh B classification) is 24mg/26mg twice daily. It is not recommended in patients with severe hepatic impairment (Child-Pugh C classification).

Renal Impairment

No dose adjustment is required in patient with mild (eGFR 60 to 90 mL/min/1.73m²) 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 24mg/26mg twice daily.

OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be peripheral vasodilation, hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If hypotension occur, supportive treatment should be instituted. It is unlikely removed by hemodialysis because of high protein binding.

DOSAGE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION

Sacuvia 50mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.
Sacuvia 100mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.
Sacuvia 200mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.

سکوویا™

(سیکوبِٹرل + والسرٹان)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔

بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔

خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
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www.highnoon-labs.com

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