Sacutan

(Sacubitril/Valsartan) Tablets

سیکوٹان

(سیکوبٹرل/ویلسارٹن) ٹیبلیٹس

Sacutan Tablets 24mg/26mg
Each film coated tablet contains:
Sacubitril..24mg
Valsartan..26mg
(as Sacubitril Valsartan sodium salt complex)
Finished Product Specs.: Innovator's Specifications.

Sacutan Tablets 49mg/51mg
Each film coated tablet contains:
Sacubitril..49mg
Valsartan..51mg
(as Sacubitril Valsartan sodium salt complex)
Finished Product Specs.: Innovator's Specifications.

Sacutan Tablets 97mg/103mg
Each film coated tablet contains:
Sacubitril...97mg
Valsartan..103mg
(as Sacubitril Valsartan sodium salt complex)
Finished Product Specs.: Innovator's Specifications.

Warning: Fetal Toxicity

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

CLINICAL PHARMACOLOGY

Mechanism of Action

Sacubitril / 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 / 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 antihypertrophic and antifibrotic 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 remodeling.

PHARMACOKINETICS

Absorption

Following oral administration, this medicinal product dissociates into Sacubitril and Valsartan. Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of Sacubitril, LBQ657 and Valsartan are reached in 2 hours, 1 hour and 2 hours respectively.The oral absolute bioavailability of Sacubitril and Valsartan is estimated to be more than 60% and 23%, respectively. Following twice-daily dosing of Sacubitril / Valsartan, steady state levels of Sacubitril, LBQ657 and Valsartan are reached in 3 days. At steady state Sacubitril and Valsartan do not accumulate significantly whereas LBQ657 accumulates by 1.6-fold. Administration with food has no clinically singnificant effect in the systemic exposures of Sacubitril, LBQ657 or Valsartan. Sacubitril / Valsartan can be administered with or without food.

Distribution

Sacubitril LBQ657 and Valsartan are highly bound to plasma proteins (94% to 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 volumes of distribution of Valsartan and Sacubitril are 75L and 103L respectively.

Metabolism

Sacubitril is readily converted to LBQ657 by esterases; 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%).

Elimination

Following oral administration, 52% to 68% of Sacubitril (primarily as LBQ657) and ~13% of Valsartan and its metabolites are excreted in urine: 37% to 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($T_{1/2}$) of approximately 1.4 hours, 11.5 hours and 9.9 hours respectively.

Special Populations

Elderly Patients

LBQ657 and Valsartan exposure are increased in subjects over 65 years of age by 42% and 30% respectively, compared to younger subjects.

Impaired Renal Function

The exposure of LBQ657 in patients with moderate (30 ml/min/1.73 m^2≤ eGFR <60 ml/min/1.73 m^2) and severe renal impairment (15 ml/min/1.73 m^2≤ eGFR <30 ml/min/1.73 m^2) was 1.4-fold and 2.2-fold higher compared to patients with mild renal impairment (60 ml/min/1.73m^2≤ eGFR <90 ml/min/1.73 m^2). The exposure of Valsartan was similar in patients with moderate and severe renal impairment compared to patients with mild renal impairment.

Impaired Hepatic Function

In patients with mild to moderate hepatic impairment, the exposures of Sacubitril are increased by 1.5 and 3.4-fold, LBQ657 increased by 1.5 and 1.9-fold and Valsartan are increased by 1.2-fold and 2.1-fold, respectively, compared to healthy subjects. However, in patients with mild to moderate hepatic impairment, the exposures of free concentrations of LBQ657 increased by 1.47 and 3.08-fold respectively and the exposures of free concentrations of Valsartan increased by 1.09-fold and 2.20-fold, respectively, compared to healthy subjects. Sacubitril / Valsartan has not been studied in patients with severe hepatic impairment.

THERAPEUTIC INDICATIONS

Sacutan (Sacubitril / Valsartan) is indicated in adult patients for treatment of symptomatic chronic heart failure (NYHA Class II-IV) with reduced ejection fraction. Sacutan (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 Sacutan (Sacubitril / Valsartan) is one tablet of 49mg / 51mg twice daily. The dose of Sacutan (Sacubitril / Valsartan) should be doubled after 2 to 4 weeks to the target maintenance dose of one tablet of 97mg / 103mg twice daily, as tolerated by the patient.
If patients who experience tolerability issues (systolic blood pressure ≤ 95mmHg, symptomatic hypotension, hyperkalemia, renal dysfunction),consideration should be given to adjustment of concomitant medications or to temporary down-titration or discontinuation of (Sacubitril / Valsartan).

Starting dose of Sacutan of 24mg / 26mg for some populations

A starting dose of Sacutan (Sacubitril / Valsartan) of one tablet of 24mg / 26mg taken twice daily is recommended for patients not currently taking an ACE inhibitor or an ARB or patients previously taking low doses of these agents. A starting dose of Sacutan (Sacubitril / Valsartan) of one tablet of 24mg / 26mg taken twice daily should be considered for patients who have risk factors for hypotension, including patients ≥ 75 years old and patients with low systolic blood pressure (SBP ≥ 100 to 110 mmHg). The dose of Sacutan(Sacubitril / Valsartan) should be doubled every 2 - 4 weeks to the target dose of one tablet of Sacutan (Sacubitril / Valsartan) 97mg / 103mg twice daily, as tolerated by the patient.

Renal Impairment

No dose adjustment is required in patients with mild renal impairment. A starting dose of 24mg / 26mg twice daily should be considered in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73 m^2). Sacutan (Sacubitril / Valsartan) should be used with caution in patients with severe renal impairment and a starting dose of 24mg / 26mg twice daily is recommended. There is no experience in patients with end-stage renal disease (ESRD) and therefore use of Sacutan (Sacubitril / Valsartan) is not recommended.

Hepatic Impairment

No dose adjustment is required when administering Sacutan (Sacubitril / Valsartan) to patients with mild hepatic impairment (Child-Pugh A classification). Sacutan (Sacubitril / Valsartan) should be used with caution 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 and the recommended starting dose is 24mg / 26mg twice daily. Sacutan (Sacubitril / Valsartan) is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification).

Pediatric Population

The safety and efficacy of Sacutan (Sacubitril / Valsartan) in children and adolescents aged below 18 years have not been established.

CONTRAINDICATIONS

Sacubitril / Valsartan is contraindicated in patients with:

- Hypersenitivity to the active substance, Sacubitril, Valsartan or to any of the excipient of the product.
- Concomitant use with ACE inhibitors. Sacubitril / Valsartan must not be administered until 36 hours after discontinuing ACE inhibitor therapy.
- Known history of angioedema related to previous ACE inhibitor or ARB therapy.
- Hereditary or idiopathic angioedema.
- Concomitant use with aliskiren-containing medicinal products in patients with diabetes mellitus or in patients with renal impairment (eGFR < 60 ml/min/1.73 m^2)
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy.

PRECAUTIONS

Fetal Toxicity

Sacubitril / Valsartan can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, consider alternative durg treatment and discontinue Sacubitril / Valsartan. However, if there is no appropriate alternative to therapy with drug 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. If angioedema occurs discontinue Sacubitril / Valsartan immediately, provide appropriate therapy and monitor for airway compromise. Sacubitril / Valsartan should not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy.

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 lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drug and treatment of other causes of hypotension (e.g. hypovolemia).
If hypotension persists despite such measures, reduce the dosage or temporarily discontinue Sacubitril / Valsartan.

Impaired Renal Function
As a consequence of inhibiting the renin angiotensin-aldosterone system (RAAS), decrease in renal function may be anticipated in susceptible individuals treated with Sacubitril / Valsartan . 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 monitor serum potassium periodically and treat appropriately, especially in patients, having 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 requied.

Patients with NYHA functional classification IV
Caution should be exercised when initiating Sacubitril / Valsartan in patients 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.

Patients with hepatic impairment
There is limited clinical experience in patients with moderate hepatic impairment (Child-Pugh B classification). Caution is therefore recommended when using in these patients.

Ability to drive and use machine
When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

Nursing Mothers
It is not known whether Sacubitril / Valsartan is excreted in human milk, because of the potential risk for adverse reactions in breast-feed newborns/infants, therefore it is not recommended during breast-feeding. A decision should be made whether to abstain from breast-feeding or to discontinue Sacubitril / Valsartan while breast-feeding, taking into account the importance of Sacubitril / Valsartan to the mother.

ADVERSE REACTIONS
Very Common
Hyperkalemia, hypotension, and renal impairment.

Common
Anemia, hypokalemia, hypoglycemia, dizziness, headache, syncope, vertigo, orthostatic hypotension, cough, diarrhea, nausea, gastritis, renal failure, fatigue and asthenia.

Uncommon
Hypersensitivity, dizziness postural, pruritus, rash and angioedema.

DRUG INTERACTIONS
Angiotensin Receptor Blockers
Sacubitril / Valsartan should not be co-administered with another ARB containing product.

QATP1B1 and OATP1B3 substrates, e.g. statins
Sacubitril inhibits OATP1B1 and OATP1B3 transporters. Therefore, it may 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. Caution should be exercised when sildenafil or another PDE5 inhibitor is initiated in patients treated with Sacubitril / Valsartan.

Potassium
Concomitant use of potassium-sparing diuretics (triamterene, amiloride), mineralocorticoid antagonists (e.g. spironolactone, eplerenone), potassium supplements, salt substitutes containing potassium or other agents (such as heparin) may lead to increase in serum potassium and to increase in serum creatinine. Monitoring of serum potassium is recommended if Sacubitril / Valsartan is co-administered with these agents.

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors.
In elderly patients, volume-depleted patients (including those on diuretic therapy) or patients with compromised renal function, concomitant use of Sacubitril / Valsartan and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying treatment in patients on Sacubitril / Valsartan who are taking NSAIDs concomitantly.

Lithium
Reversible increase in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists. Therefore, this combination is not recommended.
If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased further.

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, cyclosporin), 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.

Metformin HCl
Co-administration of Sacubitril / Valsartan with metformin reduced both C_{max} 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.

OVERDOSAGE
In healthy volunteers, a single dose of 583mg Sacubitril / 617mg Valsartan and multiple doses of 437mg Sacubitril / 463mg 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 / Valsartan. Symptomatic treatment should be provided. Sacubitril / Valsartan is unlikely to be removed by hemodialysis because of high protein binding.

STORAGE
Store below 30°C.
Protect from heat, light and moisture.

PRESENTATION
Sacutan (Sacubitril / Valsartan) Tablets 24mg / 26mg is available in pack of 14's.
Sacutan (Sacubitril / Valsartan) Tablets 49mg / 51mg is available in pack of 14's.
Sacutan (Sacubitril / Valsartan) Tablets 97mg / 103mg is available in pack of 14's.

Keep all medicines out of the reach of children.

To be sold on prescription of a registered medical practitioner only.

Manufactured by :
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