Name of the product: Sacuval Tablets
Size of the insert (138x225)mm front & back printing

SACUVAL TABLETS

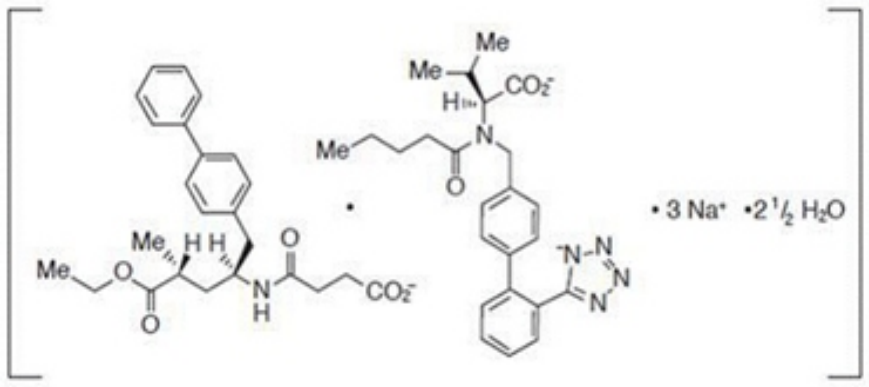
(Sacubitril / Valsartan)

سیکیوال ٹیبلٹس

Film Coated Tablets: Sacubitril/Valsartan…..... 24/26mg; 49/51mg; 97/103mg

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

DESCRIPTION:
SACUVAL (sacubitril and valsartan) is a combination of a neprilysin inhibitor and an angiotensin II receptor blocker. Its empirical formula (hemipentahydrate) is C48H55N6O8Na3 2.5 H2O. Its molecular mass is 957.99 and its schematic
structural formula is:



CLINICAL PHARMACOLOGY
Pharmacodynamics:
Mechanism of Action
SACUVAL contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. SACUVAL 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 SACUVAL 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
Absorption
Following oral administration, SACUVAL 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%. The valsartan in SACUVAL is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in SACUVAL is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.

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 75 and 103 L, 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 (T1/2) of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively.

INDICATIONS AND USAGE
SACUVAL is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, 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.
SACUVAL is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

CONTRAINDICATIONS
- Hypersensitivity to any component.
- History of angioedema related to previous ACE inhibitor or ARB therapy.
- Concomitant use with ACE inhibitors.
- Concomitant use with aliskiren in patients with diabetes.

WARNINGS AND PRECAUTIONS
- Observe for signs and symptoms of angioedema and hypotension.
- Monitor renal function and potassium in susceptible patients.

ADVERSE REACTIONS
Adverse reactions occurring ≥5% are hypotension, hyperkalemia, cough, dizziness, and renal failure.

DRUG INTERACTIONS
- Dual blockade of the renin-angiotensin system: Do not use with an ACEi, do not use with aliskiren in patients with diabetes, and avoid use with an ARB.
- Potassium-sparing diuretics: May lead to increased serum potassium.
- NSAIDs: May lead to increased risk of renal impairment.
- Lithium: Increased risk of lithium toxicity.

USE IN SPECIFIC POPULATIONS
- Pregnancy: SACUVAL can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, consider alternative drug treatment and discontinue SACUVAL.
- Lactation: Breastfeeding or drug should be discontinued.
- Severe Hepatic Impairment: Use not recommended.

DOSAGE AND ADMINISTRATION
- The recommended starting dose of SACUVAL is 49/51 mg (sacubitril/valsartan) twice-daily. Double the dose of SACUVAL 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
  - patients with moderate hepatic impairment
- Double the dose of SACUVAL every 2 to 4 weeks to the target maintenance dose of 97/103 mg (sacubitril/valsartan) twice-daily, as tolerated by the patient.

PRECAUTIONS:
Avoid direct sunlight and protect from moisture and heat. Store below 25°C. Keep all medicines out of the reach of children. To be sold and used on the prescription of Registered Medical Practitioners only.

PRESENTATION:
Sacuval 24/26mg, 49/51mg & 97/103mg Tablets are available in Packing of 14 film coated tablets each.

عمومی خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: دھوپ، نمی اور گرمی سے بچائیں۔ 25 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

Complete Medical Information only for doctors on request.

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