CUBIL

(Sacubitril / Valsartan)
Tablets

50mg
100mg
200mg

کیوبل ۵۰ ملی گرام
۱۰۰ ملی گرام
۲۰۰ ملی گرام فلمکلس

QUALITATIVE AND QUANTITATIVE COMPOSITION

Cubil 50mg tablets
Each film- coated tablet contains:
Sacubitril 24mg
Valsartan 26mg
Innovator's Specs.
Cubil 100mg tablets
Each film- coated tablet contains:
Sacubitril 49mg
Valsartan 51mg
Innovator's Specs.
Cubil 200mg tablets
Each film- coated tablet contains:
Sacubitril 97mg
Valsartan 103mg
Innovator's Specs.

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

DESCRIPTION

Cubil (Sacubitril and Valsartan) is a combination of a neprilysin inhibitor and an angiotensin II receptor blocker. Cubil 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. Cubil is available as film-coated tablets for oral administration, containing 24mg of Sacubitril and 26mg of Valsartan; 49mg of Sacubitril and 51mg of Valsartan; 97mg of Sacubitril and 103mg of Valsartan.

CLINICAL PHARMACOLOGY

Mechanism of Action: Cubil contains a neprilysin inhibitor, Sacubitril, and an angiotensin receptor blocker, Valsartan. Cubil 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.

Pharmacodynamics: The cardiovascular and renal effects of Cubil 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 AT1receptor, and also inhibits angiotensin II-dependent aldosterone release.

Blood Pressure: Addition of a 50mg single dose of sildenafil to Cubil at steady state (194mg Sacubitril/206mg 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 Cubil alone. Co-administration of Cubil did not significantly alter the BP effect of intravenous nitroglycerin.

Pharmacokinetics: Absorption: Following oral administration, Cubil 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 Cubil is more bioavailable than the Valsartan in other marketed tablet formulations; 26mg, 51mg, and 103mg of Valsartan in Cubil is equivalent to 40mg, 80mg, and 160mg of Valsartan in other marketed tablet formulations, respectively. Following twice-daily dosing of Cubil, 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. Cubil administration with food has no clinically significant effect on the systemic exposures of Sacubitril, LBQ657, or Valsartan. Cubil can therefore 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 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

Heart Failure: Cubil 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. Cubil is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

CONTRAINDICATIONS

Cubil 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.

INTERACTIONS

Dual Blockade of the Renin-Angiotensin-Aldosterone System: Concomitant use of Cubil with an ACE inhibitor is contraindicated because of the increased risk of angioedema. Avoid use of Cubil with an ARB, because Cubil contains the angiotensin II receptor blocker Valsartan. The concomitant use of Cubil 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.

Non-steroidal 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 Cubil 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 Cubil.

USE IN SPECIAL POPULATION

Pregnancy: Cubil 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.

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.

Lactation: 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. 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 Cubil.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: The dose should be in line with the renal function of the elderly patient.

Hepatic Impairment: Cubil is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis (Child-Pugh C classification).

Renal Impairment: No dose adjustment is required in patients with mild (eGFR 60 to 90 ml/min/1.73 m2) to moderate (eGFR 30 to 60 ml/min/1.73 m2) renal impairment.

PRECAUTIONS

Patients with NYHA functional classification I.V.: Caution should be exercised when initiating Cubil in patients with NYHA functional classification I.V.

B-type natriuretic peptide (BNP): BNP is not a suitable biomarker of heart failure in patients treated with Cubil because it is a neprilysin substrate.

Fetal Toxicity: Cubil can cause fetal harm when administered to a pregnant woman.

Angioedema: Cubil may cause angioedema. If angioedema occurs, discontinue Cubil immediately, provide appropriate therapy, and monitor for airway compromise. Cubil 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.

Hypotension: Cubil 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.

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 Cubil. As with all drugs that affect the RAAS, Cubil 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: Treatment should not be initiated if the serum potassium level is >5.4 mmol/l. Through its actions on the RAAS, hyperkalemia may occur with Cubil. 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 Cubil may be required.

ADVERSE REACTION

Clinically significant adverse reactions that appear in other sections of the labeling include: • Angioedema • Hypotension • Impaired Renal Function • Hyperkalemia

DOSAGE AND ADMINISTRATION

Cubil is contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. If switching from an ACE inhibitor to Cubil allow a washout period of 36 hours between administration of the two drugs. The recommended starting dose of Cubil is 49mg /51mg twice-daily. Double the dose of Cubil after 2 to 4 weeks to the target maintenance dose of 97mg /103mg twice daily, as tolerated by the patient.

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. Double the dose of Cubil every 2 to 4 weeks to the target maintenance dose of 97mg/103mg twice daily, as tolerated by the patient.

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

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). Double the dose of Cubil every 2 to 4 weeks to the target maintenance dose of 97mg/103mg twice daily, as tolerated by the patient. No starting dose adjustment is needed for mild hepatic impairment (Child-Pugh A classification). Use in patients with severe hepatic impairment is not recommended.

Overdosage: Hypotension is the most likely result of overdosage due to the blood pressure lowering effects of Cubil. Symptomatic treatment should be provided. Cubil is unlikely to be removed by hemodialysis because of high protein binding.

Missed Dose: If a dose is missed, the patient should take the next dose at the scheduled time. If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Take the next dose at your regular time.

INSTRUCTIONS:

Dosage as directed by the physician.
Store at 25°C, excursions permitted to 15°C-30°C. Protect from sunlight and moisture. Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

PRESENTATION

Cubil tablets 50mg are available in Alu-Alu blister pack of 2x7's with leaflet.
Cubil tablets 100mg are available in Alu-Alu blister pack of 2x7's with leaflet.
Cubil tablets 200mg are available in Alu-Alu blister pack of 2x7's with leaflet.

علامات/طریقہ استعمال:
کیوبل دل کے دائمی امراض میں مبتلا مریضوں کے علاج کے لئے تجویز کردہ ہے۔

مضر اثرات:
سوجن، بلڈ پریشر کا کم ہونا، گردوں میں خرابی، خون میں پوٹاشیم کی مقدار کی زیادتی۔

احتیاطی تدابیر:
کیوبل کے اندر موجود کسی بھی اجزا سے حساسیت رکھنے والے مریضوں میں کیوبل کا استعمال ممنوع ہے۔
حاملہ خواتین اور دودھ پلانے والی ماؤں میں کیوبل کا استعمال ممنوع ہے۔
بچے اور بزرگ صرف ڈاکٹر کے مشورے کے مطابق استعمال کریں۔
جگر کے مریضوں میں کیوبل کا استعمال ممنوع ہے۔
گردے کے معمولی امراض میں مبتلا مریضوں میں دوا کی مقدار کم کرنے کی ضرورت نہیں ہے۔

ہدایات:
خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۲۵ ڈگری سینٹی گریڈ پر رکھیں،
محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔
سورج کی روشنی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔

For detailed information please contact:

GENIX

GENIX PHARMA PRIVATE LIMITED
44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, Fax: +92-21-111-10-10-22
E-mail: info@genixpharma.com Web.: www.genixpharma.com

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