Cova™

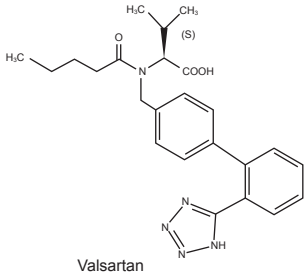
[Valsartan]

کووا

Tablets 80mg & 160mg

DESCRIPTION

Cova (Valsartan) is a nonpeptide, orally active and specific angiotensin II receptor blocker acting on the AT_1 receptor subtype. Valsartan is chemically described as N-(1-oxopentyl) -N-[[2'- (1H-tetrazol-5-yl) [1,1'-biphenyl] -4- yl] methyl]- L-valine. Its molecular formula is $C_{24}H_{29}N_9O_3$ and structural formula is:



Valsartan

QUALITATIVE AND QUANTITATIVE COMPOSITION

Cova (Valsartan) is available for oral administration as:

Cova Tablets 80mg
Each film-coated tablets contains:
Valsartan USP…80mg

Cova Tablets 160mg
Each film-coated tablets contains:
Valsartan USP…160mg

CLINICAL PHARMACOLOGY

Mechanism of Action:

Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

Pharmacokinetics

Absorption:

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%.

Effect of Food:

Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. Therefore, valsartan can therefore be given either with or without food.

Distribution:

Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Metabolism:

Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Excretion:

Valsartan shows multiexponential decay kinetics ($t_{½}\alpha$ <1h and $t_{½}\beta$ about 9h). Valsartan is primarily eliminated by biliary excretion in feces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. The half-life of valsartan is 6 hours.

Special populations

Elderly

Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young.

Renal impairment

There is no apparent correlation between renal function (measured by creatinine clearance) and systemic exposure to valsartan (measured by AUC) in patients with different degrees of renal failure.

Hepatic impairment

Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects.

Impaired renal function

Use in pediatric patients with a creatinine clearance <30 ml/min and pediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for pediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored.

THERAPEUTIC INDICATIONS

Cova (Valsartan) is indicated for the treatment of the following conditions:

- Hypertension.
- Heart failure (NYHA class II-IV) in patients receiving usual therapy (e.g. diuretics, digitalis) who are intolerant to ACE inhibitors.
- To improve survival following myocardial infarction in clinically stable patients with clinical or radiological evidence of left ventricular failure and/or with left ventricular systolic dysfunction.

DOSAGE AND ADMINISTRATION

Hypertension

The recommended dose of Cova (Valsartan) is 80mg once daily. The maximum antihypertensive effect is seen after 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 160mg. If additional blood pressure reduction is required, a diuretic may be added or the dose can be increased further to a maximum of 320mg. Cova (Valsartan) also be administered with other antihypertensive agents.

Heart failure

The recommended starting dose of Cova (Valsartan) is 40mg twice daily. Titration upwards to 80mg and 160mg twice daily should be done to the highest dose tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered is 320mg in divided doses.
An assessment of renal function should always be conducted in patients with heart failure.

Post-myocardial infarction

Therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20mg twice daily, valsartan therapy should be titrated to 40mg, 80mg, and 160mg twice daily over the next few weeks. The starting dose is provided by the 40mg divisible tablet.
Achievement of the target dose of 160mg twice daily should be based on the patient's tolerability to valsartan during titration. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction. Evaluation of post-myocardial infarction patients should always include assessment of renal function. Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta-blockers and statins.

Special Population:

Renal impairment

For patients with severe renal impairment, a maximum daily dose of 80mg per day is recommended.

Hepatic impairment

A daily dose of 80mg should not be exceeded.

Pediatric population

Children and adolescents 6 to 18 years of age

The initial dose is 40mg once daily for children weighing below 35kg and 80mg once daily for those weighing 35kg or more. The dose should be adjusted based on blood pressure response.

Use in pediatric patients aged 6 to 18 years with renal impairment

Use in pediatric patients with a creatinine clearance <30 ml/min and pediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for pediatric patients with a creatinine clearance >30ml/min. Renal function and serum potassium should be closely monitored.

Use in pediatric patients aged 6 to 18 years with hepatic impairment

As in adults, valsartan is contraindicated in pediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. The dose of valsartan should not exceed 80mg in pediatric patients.

Pediatric heart failure and recent myocardial infarction

Valsartan is not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.

CONTRAINDICATIONS

Valsartan is contraindicated in patients with:

- Patients with known hypersensitivity to valsartan or to any excipient of the product.
- Patients with severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy.
- The concomitant use of valsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2).

ADVERSE EFFECTS:

Common

Viral infections, neutropenia, hyperkalemia, dizziness, postural dizziness, vertigo, hypotension, orthostatic hypotension, renal failure and impairment.

Uncommon

Upper respiratory tract infection, pharyngitis, sinusitis, insomnia, decreased libido,

syncope, vertigo, cardiac failure, hypotension, cough, diarrhea, abdominal pain, back pain, fatigue, asthenia, headache and oedema.

Rare
Dizziness

PRECAUTIONS
Hyperkalemia
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Sodium- and/or volume-depleted patients
In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with valsartan.
Sodium and/or volume depletion should be corrected before starting treatment with valsartan, for example by reducing the diuretic dose.

Renal artery stenosis
In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of valsartan has not been established. However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with valsartan as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis or hypertrophic obstructive cardiomyopathy (HOCM).

Impaired renal function
Valsartan should be used with caution in the patients with creatinine clearance <10 ml/min and patients undergoing dialysis.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, valsartan should be used with caution.

Other conditions with stimulation of the renin-angiotensin system
As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of valsartan may be associated with impairment of the renal function.

History of angioedema
Valsartan should be immediately discontinued in patients who develop angioedema and valsartan should not be re-administered.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)
Concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Pediatric population
Heart failure / Post-myocardial infarction
Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction. An assessment of renal function should always be conducted in patients with heart failure or post-myocardial infarction.

Concomitant therapy in patients with heart failure
Concurrent administration of ACE inhibitors, beta-blockers and valsartan is not recommended.

Effects on ability to drive and use machines:
As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

Nursing Mothers
It is not known whether 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 valsartan, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interaction
Lithium
Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists, including valsartan. Monitor serum lithium levels during concomitant use.

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Transporters
Co-administration of inhibitors of the uptake transporter (eg. rifampin, ciclosporin) or efflux transporter (eg. ritonavir) may increase the systemic exposure to valsartan. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

Pediatric population
In hypertension, in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

OVERDOSAGE
Symptoms
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms; stabilisation of the circulatory condition is of prime importance. If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken. Valsartan is unlikely to be removed by hemodialysis.

STORAGE
Store at 25°C (Excursions permitted between 15°C to 30°C).
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Cova (Valsartan) Tablets 80mg are available in pack of 14's.
Cova (Valsartan) Tablets 160mg are available in pack of 14's.

Keep out of reach of children.

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

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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