For the use only of a Registered Medical Practitioner

PRESCRIBING INFORMATION

STARVAL

(Valsartan Tablets)

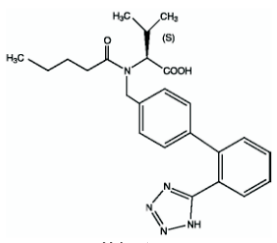
COMPOSITION

STARVAL TABLETS 80 mg
Each film-coated tablet contains:
Valsartan USP……..80 mg

STARVAL TABLETS 160 mg
Each film-coated tablet contains:
Valsartan USP……..160 mg

DESCRIPTION

STARVAL contains Valsartan**.** 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 empirical formula is $C_{24}H_{29}N_5O_3$, its molecular weight is 435.5, and its structural formula is



Valsartan

PRODUCT DESCRIPTION

For 80 mg strength: Orange colored, film coated, oval tablets debossed with **'V&2'** on either side of breakline on one side and breakline on the other side.

For 160 mg strength: Pink colored, film coated, oval tablets debossed with **'V&1'** on either side of breakline on one side and breakline on the other side.

PHARMACOLGY

- **Pharmacodynamics**

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. 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.
There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one-200th that of valsartan itself.
Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.
Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.
Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In reported multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In reported multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

- **Pharmacokinetics**

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

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.

Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that reported in healthy volunteers. AUC and C_{max} values of valsartan are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

Special populations

Elderly
A somewhat higher systemic exposure to valsartan can occur in some elderly subjects than in young subjects; however, this does not have any clinical significance.

Impaired renal function
As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation exists between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance>10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see **DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS**). Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation and, as expected systemic exposure to valsartan is not correlated with the degree of liver dysfunction. No dose adjustment for valsartan is therefore necessary in patients with hepatic insufficiency of non-biliary origin and without cholestasis. The AUC with valsartan has been observed to approximately double in patients with biliary cirrhosis or biliary obstruction.

INDICATIONS / USAGE

Hypertension
Treatment of hypertension

Post- myocardial infarction
Valsartan is indicated to improve survival following myocardial infarction in clinically stable patients with signs, symptoms or radiological evidence of left ventricular failure and /or with left ventricular systolic dysfunction.

Heart Failure
Treatment of heart failure (NYHA class II-IV) in patients receiving usual therapy (such as diuretics, digitalis) who are intolerant to ACE inhibitors.

Valsartan improves morbidity in these patients, primarily via reduction in hospitalisation for heart failure. Valsartan also slows the progression of heart failure, improves NYHA functional class, ejection fraction and signs and symptoms of heart failure and improves quality of life versus placebo.

DOSAGE AND ADMINISTRATION

Hypertension
The recommended dose of valsartan is 80 mg or 160mg once daily, irrespective of race, age, or gender. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 320 mg, or a diuretic may be added.
Valsartan may also be administered with other antihypertensive agents.

Post myocardial infarction
Therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan should be titrated to 40 mg, 80 mg, and 160 mg twice daily over the next few weeks.

The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose be achieved by three months, 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.

Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers or statins.

Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Heart failure
The recommended starting dose of valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg 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 in reported clinical trials is 320 mg in divided doses. Evaluation of patients with heart failure should always include assessment of renal function.

NOTE for all indications: No dosage adjustment is required for patients with renal impairment or for patients with hepatic insufficiency of non biliary origin and without cholestasis.

Use in children and adolescents
The safety and efficacy of valsartan have not been established in children and adolescents (below the age of 18 years).

STARVAL TABLETS (containing valsartan) are available in only two strengths of 80mg and 160mg. They are not able to deliver all approved dose regimens of valsartan; other approved dosage forms and strengths of valsartan should be used in such cases.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Pregnancy.

WARNINGS AND PRECAUTIONS

Hyperkalaemia
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.

Short-term administration of valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). 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.

Kidney transplantation
There is currently no experience on the safe use of valsartan in patients who have recently undergone kidney transplantation.

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
No dosage adjustment is required for patients with a creatinine clearance >10 ml/min. There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see **PHARMACOLGY; Pharmacokinetics**).

Hepatic impairment
No dosage adjustment is required for patients with hepatic insufficiency. Valsartan is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower valsartan clearance. Particular caution should be exercised when administering valsartan to patients with biliary obstructive disorders (see **PHARMACOLGY; Pharmacokinetics**).

Recent myocardial infarction
The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies. Therefore, the combination of valsartan with an ACE inhibitor is not recommended.
Caution should be observed when initiating therapy in post-myocardial infarction patients.

Evaluation of post-myocardial infarction patients should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**).

Use of valsartan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see **DOSAGE AND ADMINISTRATION**).

Heart Failure
In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and valsartan has not shown any clinical benefit. This combination apparently increases the risk for adverse events and is therefore not recommended.
Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**).

Use of valsartan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see **DOSAGE AND ADMINISTRATION**).

In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. 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.

- **Effects on ability to drive and use machines**

No studies on the effects on the ability to drive have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

DRUG INTERACTIONS

Concomitant use not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels

If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with 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.

Others
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

CYP450 interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP450 isoenzymes. The inhibitory or induction potential of valsartan on CYP450 is also unknown.

Transporters: Coadministration of inhibitors of the uptake transporter (rifamipin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

ADVERSE REACTIONS / SIDE EFFECTS

The ADRs associated with valsartan are consistent with its pharmacology. Incidence of ADRs does not appear to be related to dose or treatment duration and also there is no association with gender, age or race.

The ADRs reported with valsartan therapy are listed below according to system organ class.

Hypertension	
Blood and lymphatic system disorders	
Not known	Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Increase of serum potassium
Ear and labyrinth system disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary Disorders	
Not known	Elevation of liver function values including increase of serum bilirubin.
Skin and subcutaneous tissue disorders	
Not known	Angioedema, Rash, Pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, Elevation of serum creatinine
General disorders and administration site conditions	
Uncommon:	Fatigue

The safety profile in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile reported in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in post-myocardial infarction and/or heart failure patients are listed below:

Post-myocardial infarction and/or heart failure	
Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia
Not known	Increase of serum potassium
Nervous system disorders	
Common	Dizziness, Postural dizziness
Uncommon	Syncope, Headache
Ear and labyrinth system disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Cardiac failure
Vascular disorders	
Common	Hypotension, Orthostatic hypotension
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Nausea, Diarrhoea
Hepatobiliary Disorders	
Not known	Elevation of liver function values
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema
Not known	Rash, Pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Common	Renal failure and impairment
Uncommon	Acute renal failure, Elevation of serum creatinine
Not known	Increase in Blood Urea Nitrogen
General disorders and administration site conditions	
Uncommon	Asthenia, Fatigue

Other reported adverse effects
Viral infections, sinusitis, pharyngitis, edema, arthralgia, palpitations, constipation, dry mouth, dyspepsia, diarrhea, flatulence, back pain, muscle cramps, anxiety, insomnia, paresthesias, somnolence, dyspnea, impotence, chest pain, anorexia, alopecia, rhabdomyolysis, libido decrease rhinitis.

USE IN SPECIAL POPULATIONS

- **Pregnancy**

Due to the mechanism of action of angiotensin II antagonists, a risk for the fetus cannot be excluded. In utero exposure to ACE inhibitors (a specific class of drugs acting on the RAAS) during the second and third trimesters has been reported to cause injury and death to the developing fetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohyramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan. As for any drug that also acts directly on the RAAS, valsartan should not be used during pregnancy or women planning to become pregnant. Healthcare proffesionals prescribing any agents acting on the RAAS should counsel women on childbearing potential about potential risk of these agents during pregnancy. If pregnancy is detected during therapy, valsartan should be discontinued as soon as possible.

- **Lactation**

Because no information is available regarding the use of valsartan during breastfeeding, valsartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

- ***Pediatrics***

Valsartan is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

- ***Geriatrics***

No dose adjustment is required in elderly patients.

- **Renal impairment**

No dosage adjustment is required for patients with a creatinine clearance >10 ml/min (see **WARNINGS AND PRECAUTIONS and PHARMACOLGY; Pharmacokinetics**).

- **Hepatic impairment**

About 70% of the absorbed dose is excreted in the bile mainly as unchanged compound. Valsartan does not undergo extensive biotransformation, and, as expected systemic exposure to valsartan is not correlated with the degree of liver dysfunction. No dose adjustment for valsartan is therefore necessary in patients with hepatic insufficiency of non-biliary origin and without cholestasis hepatic cholestasis. The AUC with valsartan has been observed to approximately double in patients with biliary cirrhosis or biliary obstruction (see **WARNINGS AND PRECAUTIONS and PHARMACOLGY; Pharmacokinetics**).

OVERDOSAGE

Symptoms
Overdose with valsartan may result in marked hypotension, which could lead to depressed levels 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 haemodialysis.

STORAGE: Store at a temperature below 30°C, protected from moisture.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

SUPPLY: Blister pack of 10's, Box of 3x10's

Date of Revision: April 2016

5118930

Manufactured in India by:
Sun Pharmaceutical Ind. Ltd.
Paonta Sahib, Dist. Sirmour
H.P. -173 025

Product Registration Holder:
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08000 Sungai Petani, Kedah, Malaysia

Font Size : 6.5 pt.

PTT–PACKAGING PAONTA

Description:	Starval 80/160 mg tablets (PIL)
Market:	Malaysia
Dimensions:	140x400 mm
New SAP Code:	5118930
Old SAP Code:	5092457
Pharma Code:	18930
Revision date:	15.07.2015/ 06.04.2016

Colours

Black