PACKAGE INSERT TEMPLATE FOR VALSARTAN TABLET

Brand or Product Name

[Product name] Tablet 40mg
[Product name] Tablet 80mg
[Product name] Tablet 160mg
[Product name] Tablet 320mg

Name and Strength of Active Substance(s)

Valsartan 40mg
Valsartan 80mg
Valsartan 160mg
Valsartan 320mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc)
eg :Tablet - White, circular flat beveled edge film-coated tablets marked '100' on one side]

Pharmacodynamics

Angiotensin II antagonist.

The active hormone of the renin-angiotensin-aldosterone system (RAAS) is angiotensin II, which is formed from angiotensin I through ACE. Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety of physiological effects, including in particular both direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor response. In addition, it promotes sodium retention and stimulation of aldosterone secretion.

Valsartan is an orally active, potent and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with cough. Valsartan does

not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Pharmacokinetics

Absorption of valsartan after oral administration is rapid, although the amount absorbed varies widely. Mean absolute bioavailability for valsartan is 23%. Valsartan shows multiexponential decay kinetics (t½ alpha <1 hour and t½ beta about 9 hours).

The pharmacokinetics of valsartan are linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration, and little accumulation when dosed once daily. Plasma concentrations were observed to be similar in males and females.

Valsartan is highly bound to serum protein (94-97%), mainly serum albumin. Steady-state volume of distribution is low (about 17 L). Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h). Of the absorbed dose of valsartan, 70% is excreted in the faeces and 30% in the urine, mainly as unchanged compound.

When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48%, although from about 8 hours post dosing, plasma valsartan concentrations are similar for the fed and fasted group. However, this reduction in AUC is not accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and 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.

Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects compared to young subjects; however, this has not been shown to 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 was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment. No studies have been performed in patients undergoing dialysis. However, valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

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. The AUC with valsartan has been observed to approximately double in patients with biliary cirrhosis or biliary obstruction.

Indication

Hypertension
Treatment of hypertension.

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.

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.

Recommended Dosage

Hypertension

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

Heart failure

The recommended starting dose of valsartan is 40 mg film-coated tablet twice daily. Up titration 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 clinical trials is 320 mg in divided doses. Evaluation of patients with heart failure should always include assessment of renal function.

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 therapy should be titrated to 40 mg, 80 mg, and 160 mg film-coated tablet twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet.

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 occur, 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.

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).

Method of administration
Valsartan tablets may be taken independently of a meal and should be administered with water.

Mode of Administration
Oral

Contraindications
Known hypersensitivity to valsartan or to any of the excipients of valsartan.
Pregnancy

Warnings and Precautions

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. If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Renal artery stenosis

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, since other drugs that affect the renin-angiotensin-aldosterone system (RAAS) may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring of both parameters is recommended as a safety measure.

Impaired renal function

No dosage adjustment is required for patients with renal impairment. However, no data is available for severe cases (creatinine clearance <10 mL/min.), and caution is therefore advised.

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.

Heart failure / Post-myocardial infarction

Use of valsartan in patients with heart failure or post-myocardial infarction commonly results in

some reduction in blood pressure, but discontinuation of valsartan therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed.

Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction.

As a consequence of the inhibition of the RAAS, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the RAAS, treatment with ACE inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

In patients with heart failure, caution should be observed with the triple combination of an ACE inhibitor, a beta blocker and valsartan.

Effects on ability to drive and use machines

As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

Interactions with Other Medicaments

No drug interactions of clinical significance have been found. Compounds which have been studied in clinical trials include cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide.

As valsartan is not metabolised to a significant extent, clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, *in vitro* studies have not shown any interaction at this level with a range of molecules which are also highly protein bound, such as diclofenac, furosemide, and warfarin.

Potassium
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 and in heart failure patients to increases in serum creatinine. If comedication is considered necessary, caution is advisable.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)
When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Statement on Usage During Pregnancy and Lactation

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, oligohydramnios 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 in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, Valsartan should be discontinued as soon as possible.

Lactation

It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats. Thus, it is not advisable to use Valsartan in lactating mothers.

Adverse Effects / Undesirable Effects

In controlled clinical studies in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

<u>Hypertension</u>

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 following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Arthralgia, asthenia, back pain, diarrhoea, dizziness, headache, insomnia, libido decrease, nausea, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Post-myocardial infarction and/or heart failure

The safety profile seen in controlled-clinical studies in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may

relate to the patients underlying disease. ADRs that occurred in postmyocardial infarction and/or heart failure patients are listed below:

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

Hepato-biliary disorders
Not known: Elevation of liver function values

Skin and subcutaneous tissue disorders
Uncommon: Angioedema
Not known: Rash, pruritis

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

The following events have also been observed during clinical trials in patients with postmyocardial infarction and/or heart failure irrespective of their causal association with the study drug:
Arthralgia, abdominal pain, back pain, insomnia, libido decrease, neutropenia, oedema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Overdose and Treatment

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be i.v. infusion of normal saline solution. Valsartan is unlikely to be removed by haemodialysis.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size eg
Tablet - Alu-alu blister of 10s X 10/box, HDPE bottle of 30s/box]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]