Artwork Document Information	Artwork Type [Please Tick /]	Sign / Stamp
Product : T - VYTAN TABLET [FRONT] SAP No. : Date : 23 June 2025	☐ Unit Box ☑ Leaflet ☐ Aluminium Foil ☐ Generic Box ☐ Outer Box ☐ Fix-A-Form ☐ Sachet ☐ Label ☐ Shipper Carton ☐ Others : _____	

Document Category [Please Tick /]	Pharmacode / QR Code / Others Info
☑ RA/NPRA Artwork ☐ Recirculation Artwork ☐ Approval Copy Artwork ☐ Clean Copy ☐ Internal Artwork Circulation ☐ Previous Approved Artwork ☐ Draft Artwork ☐ Others : _____	

Remarks	Colour
1. Font : Arial Narrow Regular (Spacing -4.4pt / Size - 4.4pt) 2. Dimension : 150mm(w) x 179mm(h)	Black Colours shown on this proof are to indicate correct colour separations.

Vytan Tablet

Valsartan 80mg, 160mg

I. Description
Vytan Tablet 80mg - A light pink round shape film-coated tablet, slightly convex, scored at one side and plain on the other side.
Vytan Tablet 160mg - A light orange oval shape film-coated tablet, slightly convex, scored at one side and plain on the other side.

II. PHARMACOLOGY
Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC code: C09CA03

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor.
Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. 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 coughing.

Hypertension
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 antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist 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.
In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin.

Pharmacokinetics
Pharmacokinetic properties

Absorption:
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours with tablets and 1-2 hours with solution formulation. Mean absolute bioavailability is 23 % and 39 % with tablets and solution formulation, respectively. Food decreases exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (Cmax) 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.

Distribution:
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.

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 ($t_{½\alpha}$ <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.

Special populations
Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in 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 (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.
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. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Valsartan has not been studied in patients with severe hepatic dysfunction.

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

III. INDICATIONS
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 hospitalization 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.

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.

IV. CONTRAINDICATIONS
- Hypersensitivity to any of the components of Vytan;
- Pregnancy (see "Use in Pregnancy");
- Severe hepatic impairment; biliary cirrhosis and cholestasis;
- 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)

V. 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
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. No dose adjustment is required for adult patients with a creatinine clearance >10 ml/min. The concomitant use of AIIRAs, including valsartan, or of ACE inhibitors with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73 m2).

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

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Other conditions with stimulation of the renin-angiotensin system
In patients whose renal function may depend on the activity of the rennin-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.

History of angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. 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)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia 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.

Paediatric population
Impaired renal function
Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function. The concomitant use of AIIRAs, including valsartan, or of ACE inhibitors with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73 m2).

Impaired hepatic function
As in adults, Valsartan is contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. There is limited clinical experience with valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorbtion
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

VI. INTERACTIONS WITH OTHER MEDICAMENTS
Dual blockage of the Renin-Angiotensin-Aldosterone System (RAAS) with ARBs, ACE inhibitors, or aliskiren:

Concomitant use of Angiotensin II Receptor Blockers (ARBs), including valsartan, or of Angiotensin Converting Enzyme (ACE) inhibitors with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) is contraindicated.

Concomitant use not recommended

ACE inhibitors:
The use of valsartan with an ACE inhibitor may increase the risk of hyperkalaemia, hypotension, and syncope, particularly in patients with atherosclerotic disease or heart failure, or in diabetics who have end-organ damage. Such combinations should be reserved for selected cases with close monitoring of renal function.

Artwork Document Information	Artwork Type [Please Tick /]	Sign / Stamp
Product : T - VYTAN TABLET [BACK] SAP No. : Date : 23 June 2025	☐ Unit Box ☑ Leaflet ☐ Aluminium Foil ☐ Generic Box ☐ Outer Box ☐ Fix-A-Form ☐ Sachet ☐ Label ☐ Shipper Carton ☐ Others : _____	

Document Category [Please Tick /]	Pharmacode / QR Code / Others Info
☑ RA/NPRA Artwork ☐ Recirculation Artwork ☐ Approval Copy Artwork ☐ Clean Copy ☐ Internal Artwork Circulation ☐ Previous Approved Artwork ☐ Draft Artwork ☐ Others : _____	

Remarks	Colour
1. Font : Arial Narrow Regular (Spacing -4.4pt / Size - 4.4pt) 2. Dimension : 150mm(w) x 179mm(h)	Black Colours shown on this proof are to indicate correct colour separations.

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. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further.

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,indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

Paediatric 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.

VII. FERTILITY, PREGNANCY AND LACTATION
Pregnancy

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia);
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension

Breastfeeding
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.

VIII. ADVERSE EFFECTS

• 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 hyponatremia
Ear and labyrinth disorders	
Uncommon	Vertigo
Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepatobiliary disorders	
Not known	Elevation of liver function values including increase of serum bilirubin
Skin and subcutaneous tissue disorders	
Not known	Angioedema, Rash, Pruritus, Dermatitis bullous
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, Elevation of serum creatinie
General disorders and administration site condition	
Uncommon	Fatigue

• 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, hyponatremia
Nervous system disorders	
Common	Dizziness, Postural dizziness
Uncommon	Syncope,Headache
Ear and labyrinth 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, Dermatitis bullous
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

IX. DOSAGE AND ADMINISTRATION
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 80mg 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 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 20mg 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 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.

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).

Method of administration
Film-coated tablets: Valsartan may be taken independently of a meal and should be administered with water.
Route of Administration: Oral

X. OVERDOSAGE
Overdose with Vytan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. The patient should always be given a sufficient amount of activated charcoal. Otherwise, the usual treatment would be intravenous infusion of normal saline solution. Valsartan is not removed by haemodialysis.

Effects on Ability to Drive and Use Machine
This medicine may affect your ability to drive or use machines. If the tablets make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately.

XI. PRESENTATION
Vytan Tablet 80mg - A light pink round shape film-coated tablet, slightly convex, scored at one side and plain on the other side.
Vytan Tablet 160mg - A light orange oval shape film-coated tablet, slightly convex, scored at one side and plain on the other side.

XII. SHELF LIFE
Refer to carton for shelf life.

XIII. STORAGE CONDITION
Store below 30°C.
Protect from light and moisture.
Keep out of reach of children.
Jauhi daripada kanak-kanak.

XIV. AVAILABILITY
Vytan 80mg and 160mg pack in blister pack of 3x10's, 10x10's

XV. PRODUCT REGISTRATION HOLDER:
DUOPHARMA MANUFACTURING (BANGI) SDN. BHD.
Lot No. 2, 4, 6, 8 & 10, Jalan P/7, Section 13, Bangi Industrial Estate,
43650 Bandar Baru Bangi, Selangor, Malaysia.

XVI. MANUFACTURER:
DUOPHARMA MANUFACTURING (BANGI) SDN. BHD.
Lot No. 2 & 4, Jalan P/7, Section 13, Bangi Industrial Estate,
43650 Bandar Baru Bangi, Selangor, Malaysia.

Vytan 160mg - Reg No: MAL 18046154AZ
Vytan 80mg - Reg No: MAL 18046155AZ

Revision Date: June 2025
150001XXXX XX

DUOPHARMA