Professional Information for VALAZYD 40, 80 and 160

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

VALAZYD 40 mg film-coated tablets

VALAZYD 80 mg film-coated tablets

VALAZYD 160 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VALAZYD 40: Each tablet contains 40 mg valsartan.

VALAZYD 80: Each tablet contains 80 mg valsartan.

VALAZYD 160: Each tablet contains 160 mg valsartan.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

VALAZYD 40: Yellow coloured, oval shaped, bevelled edge, film-coated tablets with a break line on one side and plain on the other side.

VALAZYD 80: Pink coloured, round shaped, bevelled edge, film-coated tablets with a median line on one side and plain on the other side.

VALAZYD 160: Yellow coloured, oval shaped, bevelled edge, film-coated tablets debossed with a median line on one side and plain on the other side.

All strengths of VALAZYD contain median lines and can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Treatment of mild to moderate hypertension.

Post-myocardial infarction

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

VALAZYD is indicated for the treatment of heart failure (NYHA class II – IV).

4.2 Posology and method of administration

Posology

Hypertension

The recommended dose of VALAZYD is 80 mg or 160 mg 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, or a diuretic may be added.

VALAZYD may also be administered with other antihypertensive medicines.

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

The target 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.

VALAZYD may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, aspirin (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 VALAZYD is 40 mg 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 was 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 mild renal impairment (where the creatinine clearance is above 70 mL/min) or for patients with hepatic insufficiency of nonbiliary origin and without cholestasis.

Paediatric population

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

Method of administration

For oral administration.

4.3 Contraindications

- Hypersensitivity to valsartan or to any of the ingredients of VALAZYD listed in section 6.1.

- Pregnancy and lactation (see section 4.6).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers: These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium-sparing diuretics, such as spironolactone, triamterene and amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: concomitant administration with VALAZYD may lead to toxic blood concentrations of lithium (see section 4.5).
- The concomitant use of VALAZYD with aliskiren-containing products (see sections 4.4 and 4.5).
- Concomitantly using fluoroquinolones in moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in elderly patients.

4.4 Special warnings and precautions for use

Pregnancy

Should a woman become pregnant while receiving VALAZYD, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Hyperkalaemia

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) is contraindicated (see section 4.3).

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 after initiation of therapy with VALAZYD. Sodium and/or volume depletion should be corrected before starting treatment with VALAZYD, for example by reducing the diuretic dose.

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

Renal artery stenosis

In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of VALAZYD has not been established. Short-term administration of VALAZYD to 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 medicines that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis and monitoring of renal function is recommended when patients are treated with VALAZYD (see section 4.3).

Kidney transplantation

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

Primary hyperaldosteronism

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

VALAZYD is contraindicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM) (see section 4.3).

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 VALAZYD should be used with caution in these patients. No dose adjustment is required for adult patients with mild renal impairment (see sections 4.2 and 5.2). The concomitant use of angiotensin receptor blockers (ARBs), including VALAZYD, with aliskiren is contraindicated, as well as use of VALAZYD in patients with severe renal impairment (GFR < 30 mL/min) (see section 4.3).

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, VALAZYD should be used with caution (see section 5.2).

Valsartan is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower valsartan clearance (see section 5.2). Particular caution should be exercised when administering VALAZYD to patients with biliary obstructive disorders.

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 (see section 5.1). Therefore, the combination of VALAZYD with an ACE inhibitor is not recommended. Caution should be observed when initiating therapy in heart failure or post-myocardial infarction patients. Evaluation of post-myocardial infarction and heart failure patients should always include assessment of renal function (see section 4.2).

Use of VALAZYD 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 section 4.2).

Heart failure

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function

(including acute renal failure), may increase when VALAZYD is used in combination with an ACE inhibitor. The combination of VALAZYD, an ACE inhibitor and a beta blocker apparently increases the risk for adverse events and is therefore not recommended. Triple combination of an ACE inhibitor, a mineralocorticoid receptor antagonist and VALAZYD is also not recommended.

Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. 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 section 4.2). Use of VALAZYD 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 section 4.2).

Other conditions with stimulation of renin-angiotensin system

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with ACE inhibitors has been associated with oliguria and/or progressive uraemia and in rare cases with acute renal failure and/or death. As VALAZYD is an angiotensin II receptor blocker, it cannot be excluded that the use of VALAZYD may be associated with impairment of the renal function.
ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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 medicines, including ACE inhibitors. VALAZYD should immediately be discontinued in patients who develop angioedema and VALAZYD should not be re-administered (see section 4.3).

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 VALAZYD and aliskiren is therefore contraindicated (see sections 4.3 and 4.5).

Fluoroquinolones and ARBs

Concomitant use of fluoroquinolones and ARBs may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ARBs, whether used separately or concomitantly.

4.5 Interaction with other medicines and other forms of interaction

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with ARBs, ACE inhibitors or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) (see sections 4.3 and 4.4).
Concomitant use of ARBs, including VALAZYD, with aliskiren is contraindicated (see sections 4.3).

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. The concomitant use of VALAZYD and lithium is contraindicated (see section 4.3).

Fluoroquinolones

Concomitant use of ARBs and fluoroquinolones may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above

different mechanisms of kidney damage, is unknown (see section 4.3).

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

If a medicine that affects potassium levels is considered necessary in combination with VALAZYD, monitoring of potassium plasma levels is advised.

Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors, aspirin (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

In vitro data indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1/OATP1B3 and the hepatic efflux transporter MRP2. The clinical relevance of this finding is unknown. Co-administration of inhibitors of the uptake transporter (e.g. rifampicin, ciclosporin) or efflux transporter (e.g. ritonavir) may increase the systemic exposure to VALAZYD. Exercise appropriate care when initiating or ending concomitant treatment with such medicines.

Others

No interactions of clinical significance have been found with valsartan and any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age should use effective contraception.

Pregnancy

Safety in pregnancy has not been established (see sections 4.3 and 4.4). When pregnancy is planned or confirmed, VALAZYD should be discontinued. Medicines affecting the renin-angiotensin system, such as VALAZYD, can cause embryonal toxicity, fetal and neonatal morbidity and mortality when administered in pregnant women.

Breastfeeding

Safety during lactation has not been established (see sections 4.3 and 4.4). Because no information is available regarding the use of VALAZYD during breastfeeding, VALAZYD is contraindicated (see section 4.3). Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

No data are available on the effects of VALAZYD on fertility.

4.7 Effects on ability to drive and use machines

VALAZYD may cause side effects, such as dizziness or weariness. Caution is advised before driving a vehicle or operating machinery until the effects of VALAZYD are known.

4.8 Undesirable effects

Listed summary of adverse reactions

The following adverse reactions have been reported in hypertension, post-myocardial infarction and heart failure.

Infections and infestations

Frequent:	viral infections
Less frequent:	upper respiratory tract infection, pharyngitis, sinusitis, rhinitis

Blood and lymphatic system disorders

Frequent: neutropenia

Less frequent: thrombocytopenia

Frequency unknown: decreased haemoglobin, decreased haematocrit

Immune system disorders

Less frequent: hypersensitivity (including serum sickness)

Metabolism and nutrition disorders

Less frequent: hyperkalaemia[1, 2]

Frequency unknown: increased serum potassium, hyponatraemia

Psychiatric disorders

Less frequent: insomnia, libido decreased

Nervous system disorders

Frequent: postural dizziness[2], dizziness[3]

Less frequent: syncope[1], headache[3]

Ear and labyrinth disorders

Less frequent: vertigo

Cardiac disorders

Less frequent: cardiac failure[1]

Vascular disorders

Frequent: hypotension[3], orthostatic hypertension[2]

Less frequent: vasculitis

Respiratory, thoracic and mediastinal disorders

Less frequent: cough

Gastrointestinal disorders

Less frequent: diarrhoea, abdominal pain, nausea[3]

Hepatobiliary disorders

Frequency unknown: elevation of liver function values including increase of serum bilirubin

Skin and subcutaneous tissue disorders

Less frequent: angioedema[4], rash, pruritis, dermatitis bullous

Musculoskeletal and connective tissue disorders

Less frequent: back pain, arthralgia, myalgia

Renal and urinary disorders

Frequent: renal failure[1, 2]

Less frequent: renal impairment[3, 4], acute renal failure[4], renal insuffiency[4], elevation of serum creatinine

Frequency unknown: increase in blood urea nitrogen[1, 2]

General disorders and administration site conditions

Less frequent: fatigue, asthenia, oedema.

[1] Reported in post-myocardial infarction indication.

[2] Reported in heart failure indication.

[3] Reported more frequently in heart failure indication than in post-myocardial infarction indication.

[4] Reported more frequently in post-myocardial infarction than in heart failure indication.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of VALAZYD is important. It allows continued monitoring of the benefit/risk balance of VALAZYD. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

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 the ingestion is recent, vomiting should be induced.

Otherwise, the usual treatment would be intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken.

VALAZYD is unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Vascular medicines – Other hypotensives.

Pharmacotherapeutic group: Angiotensin II receptor blockers (ARBs), plain.

ATC code: C09CA03.

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.

The angiotensin 2 (AT_2) receptor subtype is unrelated to cardiovascular effect.
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.

5.2 Pharmacokinetic properties

Absorption

Valsartan is absorbed after oral administration, although the amount absorbed varies widely. Mean absolute bioavailability for valsartan is 23 %. 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. This reduction in AUC, however, is not accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution

Valsartan is highly bound to serum protein (94 – 97 %), mainly serum albumin. Steady-state volume of distribution after intravenous administration is low (about 17 L) indicating that valsartan is not distributed into tissues extensively.

Biotransformation

Valsartan is not biotransformed to a high extent as only about 20 % of a 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.

Elimination

Valsartan shows multiexponential decay kinetics ($t_{½}$ α < 1 hour and $t_{½}$ ß about 9 hours). 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 after IV administration, 30 % in the urine, mainly as unchanged compound. The half-life of valsartan is 6 hours.

The pharmacokinetics of valsartan is 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 are similar in males and females.

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 are almost proportional with increasing dose over the clinical dosing range (40 mg 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 patients

A 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 mild 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 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 be approximately double in patients with biliary cirrhosis or biliary obstruction (see section 4.4).

Paediatric population

In a study of 26 paediatric hypertensive patients (aged 1 to 16 years) given a single dose of a suspension of valsartan (mean: 0,9 – 2 mg/kg, with a maximum dose of 80 mg), the clearance (litres/h/kg) of valsartan was comparable across the age range of 1 to 16 years and similar to that of adults receiving the same formulation (see section 4.4).

5.3. Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate, anhydrous

Colloidal silica, anhydrous

Crospovidone

Hypromellose

Magnesium stearate (E572)

Microcrystalline cellulose (E460a)

Film-coating:

VALAZYD 40 and VALAZYD 160

Hypromellose

Iron oxide black (E172)

Iron oxide red (E172)

Iron oxide yellow (E172)

Polyethylene glycol

Titanium dioxide (E171)

VALAZYD 80

Hypromellose

Iron oxide red (E172)

Iron oxide yellow (E172)

Polyethylene glycol

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from moisture.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Silver aluminium/aluminium foil blister strips placed in an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

VALAZYD 40: 54/7.1.3/0098

VALAZYD 80: 54/7.1.3/0099

VALAZYD 160: 54/7.1.3/0100

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 July 2023

10. DATE OF REVISION OF THE TEXT

Not applicable.