PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

VASOVAN 40 film coated tablet

VASOVAN 80 film coated tablet

VASOVAN 160 film coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VASOVAN 40: Each film coated tablet contains 40 mg valsartan.

Contains sugar: anhydrous lactose 51,25 mg

VASOVAN 80: Each film coated tablet contains 80 mg valsartan.

Contains sugar: anhydrous lactose 102,50 mg

VASOVAN 160: Each film coated tablet contains 160 mg valsartan.

Contains sugar: anhydrous lactose 205,00 mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

VASOVAN 40 mg: Yellow coloured, round, biconvex, film coated tablets debossed with ‘J’ on one side and ‘40’ on the other.

VASOVAN 80 mg: Peach coloured, round, biconvex, film coated tablets, scored on one side and debossed with ‘80’ on scored side and ‘J’ on the other.

VASOVAN 160 mg: Yellow coloured, oval shaped, biconvex, film coated tablets, scored on one side and debossed with ‘160’ on scored side and ‘J’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension: Treatment of mild to moderate essential hypertension in adult patients 18 years and older.

Post-myocardial infarction:

To improve survival following a recent (12 hours – 10 days) 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).

4.2 Posology and method of administration

Posology

Hypertension:

The recommended dose of **VASOVAN** 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.

VASOVAN 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, **VASOVAN** therapy should be titrated to 40 mg, 80 mg,

and 160 mg twice daily over the next few weeks.. Another formulation should be used for patients requiring a dose of 20 mg.

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.

VASOVAN 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 **VASOVAN** 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 is 320 mg in divided doses.

Evaluation of patients with heart failure should always include assessment of renal function.

Special populations

Renal impairment:

- For patients with mild to moderate renal impairment (where the creatinine clearance is 30 to less than 90 ml/min) - No dosage adjustment is required

Hepatic impairment:

- A lower dose should be considered for patients with a history of hepatic impairment (see section 4.4).
- No initial dosage adjustment is required for patients with hepatic insufficiency of non-biliary origin and without cholestasis.
  (See section 4.4).

Paediatric population

Use in children and adolescents:

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

Method of administration:

VASOVAN may be taken independently of a meal and should be administered with water.

VASOVAN can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to valsartan or any of the excipients of **VASOVAN** (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Concomitant use of fluoroquinolones with angiotensin-converting enzyme (ACE) inhibitors or renin-angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment and in elderly patients (see section 4.4).
- Severe renal function impairment (creatinine clearance less than 30 ml/min).

- A history of angioedema related to previous therapy with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): 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 valve stenosis.
- Mitral valve stenosis
- Concomitant therapy with potassium-sparing diuretics, such as spironolactone, triamterene, and amiloride (see section 4.5).
- Porphyria.
- Lithium therapy: Concomitant administration with **VASOVAN** may lead to toxic blood concentrations of lithium (see section 4.5).
- The concomitant use of **VASOVAN** with aliskiren-containing products is contraindicated in patients with Type 2 diabetes mellitus (see section 4.4 and section 4.5).
- Concomitant use of **VASOVAN** with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73 m2) (see sections 4.5 and 5.1)

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **VASOVAN**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine. Should a woman contemplate pregnancy, the doctor should consider alternative medication. (See section 4.3 and section 4.6.)

Acute kidney injury:

Concomitant use of fluoroquinolones and angiotensin-converting enzyme (ACE) inhibitors or renin-angiotensin receptor blockers 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 ACE inhibitors/renin-angiotensin receptor blockers whether used separately and/or concomitantly.

Patients currently treated with concomitant use of ACE inhibitors/Angiotensin receptor blockers and fluoroquinolones should contact their doctor to re-evaluate their treatment.

Hypotension and electrolyte/fluid imbalance:

Sodium- and/or volume-depletion, due to excessive perspiration, vomiting, diarrhoea, prolonged diuretic therapy, dialysis or dietary salt restriction may increase the risk of symptomatic hypotension. In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, and/or patients with moderate to severe renal impairment, symptomatic hypotension may occur after initiation of therapy with **VASOVAN**. Sodium- and/or volume-depletion should be corrected before starting treatment with **VASOVAN,** or the treatment should start under close medical supervision (for example, by reducing the diuretic dose).

Patients with heart failure or post-myocardial infarction patients given **VASOVAN** commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed.

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:

Short-term administration of **VASOVAN** to patients with renovascular hypertension secondary to unilateral renal artery stenosis, did not induce any significant changes in renal haemodynamics or serum creatinine. However, since other drugs that affect the renin-angiotensin-aldosterone system 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. **VASOVAN** should not be used in patients with bilateral renal artery stenosis or unilateral renal artery stenosis of an artery to a single kidney, aortic valve stenosis, mitral valve stenosis or hypertrophic obstructive cardiomyopathy (see section 4.3).

Renal impairment:

Patients whose renal function may depend in part on the activity of the reninangiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on **VASOVAN**. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on **VASOVAN**.

No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance 30 ml/min to 90 ml/min). However, in severe cases (creatinine clearance < 30 ml/min) insufficient data are available. **VASOVAN** should not be used because of increased side effects (see section 4.3)

Hepatic impairment:

No dosage adjustment is required for patients with hepatic insufficiency of non-biliary

origin and without cholestasis. **VASOVAN** is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower valsartan clearance (see section 5.2). Caution should be exercised when using **VASOVAN** in patients with biliary obstructive disorders. **VASOVAN** is not recommended for use in patients with severe hepatic impairment.

Hyperkalaemia:

Since hyperkalaemia may occur, serum potassium concentrations should be monitored, especially in the elderly and patients with renal impairment and the concomitant use of potassium-sparing diuretics should generally be avoided (see section 4.3 and section 4.5).

Post-myocardial infarction/Heart failure:

Use of **VASOVAN** in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of **VASOVAN** 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 (see section 4.2).

In patients with heart failure, caution should be observed with concurrent administration of ACE inhibitors, beta-blockers and **VASOVAN** as an increase in mortality has been reported on this triple therapy (see section 4.5).

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. **VASOVAN** should be immediately discontinued in patients who develop angioedema, and **VASOVAN** 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 (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **VASOVAN** and aliskiren is therefore contraindicated (see section 4.3 and section 4.5).

VASOVAN should not be used concomitantly with aliskiren (see section 4.3).

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 uraemia and with acute renal failure and/or death. Evaluation of patients with heart failure should always include assessment of renal function.

Contains sugar (lactose):

Patients with the rare hereditary conditions of lactose or galactose intolerance, e.g. galactosaemia, Lapp lactase deficiency, or glucose-galactose malabsorption should not take

VASOVAN.

4.5 Interactions with other medicines and other forms of interaction

Concomitant use of fluoroquinolones and angiotensin-converting enzyme (ACE) inhibitors or renin-angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3 and section 4.4). The concomitant use of these molecules may lead to renal impairment due to altered renal haemodynamics in particular clinical situations or with other medications that affect renal glomerular filtration.

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 compared to monotherapy. It is recommended to monitor blood pressure, renal function, and electrolytes in patients on **VASOVAN** and other medicines that affect the RAAS (see section 4.3, section 4.4).
The concomitant use of **VASOVAN** with aliskiren, should be avoided in patients with renal impairment (GFR < 60 ml/min).
The concomitant use of **VASOVAN** with aliskiren is contraindicated in patients with Type 2 diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m2).
Concomitant use of potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium may lead to increased serum potassium and in heart failure patients to increase serum creatinine levels. If needed, serum potassium to be monitored. (see section 4.3).

Concurrent use of **VASOVAN** with lithium may reduce lithium clearance and result in lithium toxicity. Lithium levels should be regularly monitored (see section 4.3).
The antihypertensive effects of **VASOVAN** may be potentiated by medicines that lower blood pressure.

Increased mortality has been reported with valsartan in patients with heart failure also receiving both ACE inhibitors and beta blockers and it should be avoided in such patients. (see section 4.4).

Nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclo-oxygenase-2 inhibitors, may reduce the effect of diuretics and the antihypertensive effect of **VASOVAN**. Patients

taking NSAIDs concomitantly with **VASOVAN** should be adequately hydrated and renal function should be monitored.

Furthermore, in elderly patients, volume-depleted (including those on diuretic therapy), or with 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.

The antihypertensive effect of angiotensin II receptor antagonists, including valsartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Transporters

Valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (e.g., rifampin, ciclosporin) or efflux transporter (e.g., ritonavir) may increase the systemic exposure to valsartan.

As **VASOVAN** is not metabolised to a significant extent, clinically relevant interactions in the form of metabolic induction or inhibition of the cytochrome P450 isoenzyme system is not expected. Although valsartan is highly bound to plasma proteins, no interactions of clinical significance have been found during clinical trials with the following compounds: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

VASOVAN acts directly on the RAAS and therefore should not be used in women planning to become pregnant. Healthcare professionals prescribing **VASOVAN** should

counsel women of childbearing potential about the potential risk during pregnancy.

Women of childbearing age should ensure adequate contraception.

Pregnancy:

Safety has not been established. **VASOVAN** is not to be used in pregnancy (see section 4.3). Medicines affecting the renin-angiotensin system, such as **VASOVAN**, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is planned or confirmed, **VASOVAN** should be discontinued as soon as possible.

In case of accidental exposure to ARB therapy, appropriate foetal monitoring should be considered.

Infants whose mothers have taken VASOVAN should be closely observed for hypotension.

There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan.

Lactation:

Breastfeeding

Safety has not been established. **VASOVAN** should not be used during breastfeeding (see section 4.3).

Fertility

There is no information on the effects of VASOVAN on human fertility.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that dizziness or weariness may occur.

It is advisable to exercise caution when driving, operating machinery or performing tasks requiring alertness, until the effects of **VASOVAN** are known.

4.8 Undesirable effects

System Organ Class	Adverse Drug Reaction	Frequency
Infections and infestations	viral infections	*Frequent*
	upper respiratory tract infection, pharyngitis, sinusitis, rhinitis	*Less frequent*
Blood and the lymphatic system disorders	neutropenia	*Frequent*
	thrombocytopenia	*Less frequent*
	Haemoglobin decreased; haematocrit decreased	*Frequency unknown*
Immune system disorders	hypersensitivity including serum sickness	*Less frequent*
Metabolism and nutrition disorders	hyperkalaemia	*Less frequent*
Psychiatric disorders	insomnia, decreased libido	*Less frequent*
Nervous system disorders	postural dizziness	*Frequent*
	syncope, dizziness, headache	*Less frequent*
Eye disorders	blurred vision	*Less frequent*
Ear and labyrinth disorders	Vertigo	*Less frequent*
Vascular disorders	postural (orthostatic) hypotension	*Frequent*
	hypotension (may occur in patients with volume depletion), vasculitis	*Less frequent*
Cardiac disorders	cardiac failure	*Less frequent*
Respiratory, thoracic and mediastinal disorders	cough	*Less frequent*
Gastrointestinal	diarrhoea, abdominal pain, nausea	*Less frequent*

disorders		
Hepatobiliary disorders	Hepatitis, Liver function test abnormal including serum bilirubin increase	*Frequency unknown*
Skin and subcutaneous tissue disorders	angioedema, rash, pruritus, urticaria	*Less frequent*
	dermatitis bullous	*Frequency unknown*
Musculoskeletal, connective tissue and bone disorders	back pain, arthralgia, myalgia, rhabdomyolysis	*Less frequent*
Renal and urinary disorders	renal impairment, acute renal failure, renal insufficiency, serum creatinine increased,	*Less frequent*
	Serum urea increased	*Frequency unknown*
General disorders and administrative site conditions	fatigue, asthenia, oedema	*Less frequent*
	alopecia	*Frequency unknown*
Investigations	Elevated liver enzymes. Decreased: haemoglobin, haematocrit, white blood cells; increased: serum creatinine, potassium, total bilirubin.	*Less frequent*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the

SAHPRA website. Reporting can also be done directly to Unicorn Pharmaceuticals at:

vigilance@unicornpharma.co.za.

4.9 Overdose

Symptoms:

Overdose with **VASOVAN** may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. Bradycardia or tachycardia may also occur with **VASOVAN** overdose. If symptomatic hypotension should occur, institute supportive treatment.

Treatment:

If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be intravenous infusion of normal saline solution. It is unlikely to be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 7.1.3 Vascular medicine - other hypotensives

Valsartan is an orally active non-peptide angiotensin II receptor antagonist that selectively blocks the binding of angiotensin II to the AT_1 receptor in tissues such as vascular smooth muscle and the adrenal gland. 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.

In the renin-angiotensin system, angiotensin I is converted by angiotensin-converting enzyme (ACE) to form angiotensin II. Angiotensin II stimulates the adrenal cortex to synthesise and secrete aldosterone, which decreases the excretion of sodium and increases the excretion of potassium. Angiotensin II also acts as a vasoconstrictor in vascular smooth muscle. Valsartan blocks the vasoconstrictor and aldosterone-

secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT_1 receptor.

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.

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 greater affinity (about 20 000 fold) for the AT1 receptor than for the AT2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT1 receptor about one-200th (1/200th) that of valsartan itself.

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. The angiotensin 2 (AT2) receptor subtype is unrelated to cardiovascular effect.

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 to 6 hours. The antihypertensive effect persists for over 24 hours after dosing.

Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed. During repeated dosing,

the maximum reduction in blood pressure with any dose is generally attained within 2 to 4 weeks and is sustained during long-term therapy.

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

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

Post-myocardial infarction:

Valsartan is effective in reducing all-cause mortality after myocardial infarction.

Valsartan is also effective in reducing cardiovascular mortality, hospitalisation for heart failure, recurrent myocardial infarction and in improving time to the first morbid event of cardiovascular death.

Heart Failure:

In heart failure patients untreated with ACE inhibitors for at least 6 months, valsartan improved pulmonary capillary wedge pressure (PCWP), systemic vascular resistance (SVR), cardiac output (CO) and seated blood pressure (SBP) after 28 days of treatment.

5.2 Pharmacokinetic properties

Absorption

Valsartan is well absorbed after oral administration, with a bioavailability of approximately 23 %. Peak plasma concentrations occur 2 to 4 hours after an oral dose.

Valsartan shows multi-exponential decay kinetics ($t_{½}$ α < 1 h and $t_{½}$ β about 9 h).

The pharmacokinetics (AUC and Cmax values) 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.

Distribution

Valsartan is highly bound to serum protein (94 to 97 %), mainly serum albumin. Steady-state volume of distribution is low (about 17 ℓ) indicating that valsartan is not distributed into tissues extensively. Plasma clearance is relatively slow (about 2 ℓ/h) when compared with hepatic blood flow (about 30 ℓ/h).

Biotransformation

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 is not significantly metabolised and is excreted mainly unchanged via the bile. Following an oral dose about 70 % is excreted in the faeces and after iv administration, 30 % in urine, mainly as unchanged compound.

The mean elimination half-life is about 9 hours.

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.

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 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.

Elderly patients:

A significantly higher systemic exposure to valsartan was observed in elderly subjects than in young subjects; however, this has not been shown to have any clinical significance. Exposure (measured by AUC) to valsartan is higher by 70 % and the half-life is longer by 35 % in the elderly than in the young

Renal impairment:

Renal clearance accounts for only 30 % of total plasma clearance and no correlation is 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).

Gender:

Pharmacokinetics of valsartan does not differ significantly between males and females.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous lactose, crospovidone, magnesium stearate, microcrystalline cellulose and silica.

VASOVAN 40 and **160** also contain Opadry Yellow (consisting of hypromellose, macrogol, titanium dioxide and yellow iron oxide).

VASOVAN 80 also contains Opadry Pink (consisting of hypromellose, macrogol, titanium dioxide, red iron oxide and yellow iron oxide).

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister strips in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

2 x blister strips each containing 15 tablets are placed into a carton box (28 tablets per pack). The blister strips are comprised of aluminium foil and a multilayer base film (OPA/aluminium foil/PVC).

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

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8 REGISTRATION NUMBER(S)

VASOVAN 40: 46/7.1.3/0950

VASOVAN 80: 46/7.1.3/0951

VASOVAN 160: 46/7.1.3/0952

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 July 2017 (original approved version 1)

10 DATE OF REVISION OF THE TEXT

04 March 2024