1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS **S3**

1 NAME OF THE MEDICINE

VALGEN 40 mg Film-coated tablets

VALGEN 80 mg Film-coated tablets

VALGEN 160 mg Film-coated tablets

VALGEN 320 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg, 80 mg, 160 or 320 mg of valsartan.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

VALGEN 40 mg: Yellow, oval shaped, biconvex, film-coated tablets debossed with “VN” and “1” on either side of the score line on one side and “M” on the other side.

The tablet can be divided into equal doses.

VALGEN 80 mg: Pale red, round, biconvex, bevelled edged film-coated tablets having a score line on one side and debossed with “M” over “VN2” on other side.

The tablet can be divided into equal doses.

VALGEN 160 mg: Beige, oval-shaped, biconvex, bevelled-edge, film-coated tablets debossed with “M” to the left of the score on one side and “VN3” on the other side of the tablet.

The tablet can be divided into equal doses.

1.3.1.1 Professional Information for medicines for human use

VALGEN 320 mg: Dark grey, oval-shaped, biconvex, film-coated tablets debossed with “VN4” on one side and “M” on the other side.

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:

VALGEN 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 **VALGEN** 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.

VALGEN may also be administered with other antihypertensive medicines.

Post-myocardial infarction:

Treatment may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, **VALGEN** treatment 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.

VALGEN may be used in patients treated with other post-myocardial infarction medicines , 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 **VALGEN** 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 is 320 mg in divided doses.
Evaluation of patients with heart failure should always include assessment of renal function.

Special populations

Renal impairment:

NOTE for all indications: No dosage adjustment is required for patients with mild to moderate renal impairment (where the creatinine clearance is 30 to less than 90 mL/min).

Hepatic impairment:

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

A lower dose should be considered for patients with a history of hepatic impairment (see section 4.4).

Paediatric population:

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

Method of administration

Oral use.

VALGEN is given orally with or without food.

4.3 Contraindications

- Known hypersensitivity to valsartan or to any of the excipients of **VALGEN** (see section 6.1).
- A history of angioedema related to previous treatment 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).
- Severe renal function impairment (creatinine clearance less than 30 mL/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic valve stenosis.
- Mitral valve stenosis.
- Concomitant treatment with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers is

contraindicated in patients with moderate to severe renal impairment (creatinine clearance < 30 mL/min) and in elderly patients.

- Porphyria.
- Lithium treatment: Concomitant administration with **VALGEN** may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of **VALGEN** with aliskiren-containing medicines is contraindicated (see section 4.4).
- Concomitant use of **VALGEN** with aliskiren in patients with Type 2 diabetes mellitus (see section 4.5, subsection dual blockade of the RAAS).
- Concomitant use of **VALGEN** with aliskiren-containing medicines in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Pregnancy

Should a woman become pregnant while receiving **VALGEN** 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 not recommended. Monitoring of potassium should be undertaken as appropriate.

Impaired renal function

No dosage adjustment is required for patients with mild to moderate renal impairment (where the creatinine clearance is above 30 to ≤ 90 mL/min).

VALGEN is contraindicated in patients with severe renal function impairment (CrCl < 30mL/min).

The use of **VALGEN** with aliskiren should be avoided in patients with renal impairment (GFR < 60 mL/min) (see section 4.5, subsection dual blockade of the RAAS).

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, **VALGEN** should be used with caution (see sections 4.2 and 5.2).

No dosage adjustment is required for patients with hepatic insufficiency of non- biliary origin and without cholestasis. (see sections 4.2 and 5.2). VALGEN is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower **VALGEN** clearance (see section 5.2). Particular caution should be exercised when administering valsartan to patients with biliary obstructive disorders.

Sodium- and/or volume-depleted patients

In severely 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 treatment with **VALGEN**. Sodium and/or volume depletion should be corrected before starting treatment with **VALGEN**, 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 **VALGEN** 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 medicines 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 **VALGEN**.

Kidney transplantation

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

Primary hyperaldosteronism

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Recent myocardial infarction (only 40 mg, 80 mg and 160 mg)

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 sections 4.2 and 5.1). Therefore, the combination of valsartan as in **VALGEN** with an ACE inhibitor is not recommended.

Caution should be observed when initiating therapy in post-myocardial infarction patients.

Evaluation of post-myocardial infarction patients should always include assessment of renal function (see section 4.2).

Use of **VALGEN** 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 (only 40 mg, 80 mg and 160 mg)

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when **VALGEN** is used in combination with an ACE-inhibitor. In patients with heart failure, the triple combination of an ACE inhibitor, a beta-blocker and valsartan has not shown any clinical benefit (see section 5.1). This combination apparently increases the risk for adverse events and is therefore not recommended. Triple combination of an ACE-inhibitor, a mineralocorticoid receptor antagonist and valsartan as in **VALGEN** are 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 **VALGEN** 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 the renin-angiotensin system

In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of **VALGEN** 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 medicines including ACE inhibitors.

VALGEN 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 **VALGEN** and aliskiren is therefore contraindicated (see sections 4.3).

VALGEN should not be used concomitantly with aliskirien (see section 4.3).

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers

The concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (creatinine clearance < 30 mL/min) and in elderly patients.

Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/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.

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.

Impaired Hepatic function: As in adults, **VALGEN** is contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis (see sections 4.3 and 5.2). There is limited clinical experience with **VALGEN** in paediatric patients with mild to moderate hepatic impairment.

4.5 Interaction with other medicines and other forms of interaction

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS) with ARB, ACEIs, 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 (see sections 4.3, 4.4 and 5.1).

Concomitant use of angiotensin receptor antagonists (ARBs) – including valsartan – or of angiotensin- converting enzyme inhibitors (ACEIs) with aliskiren is contraindicated (see sections 4.3 and 4.4).

The concomitant use of **VALGEN**, with other medicines acting on the RAAS is associated with an increased incidence of hypotension, hyperkalaemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function, and electrolytes in patients on **VALGEN** and other medicines that affect the RAAS (see section 4.4).

The concomitant use of **VALGEN** with aliskiren, should be avoided in patients with renal impairment (GFR < 60 mL/min) (see section 4.4).

The concomitant use of **VALGEN** with aliskiren is contraindicated in patients with Type 2 diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) (see section 4.3).

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers 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).

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported. Concurrent use of lithium and valsartan as contained in **VALGEN**, is contraindicated. Therefore, monitoring of serum lithium levels is recommended, if needed (see section 4.3).

Potassium:

Concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium that may lead to increases in serum potassium, and in patients with heart failure to increase in serum creatinine, are contraindicated. If needed, serum potassium to be monitored.

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective Cyclooxygenase-2 Inhibitors (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, in elderly patients, volume-depleted (including those on diuretic treatment), or with compromised renal function, 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 is recommended, when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly, as well as adequate hydration of the patient.

Transporters:

In vitro data indicates 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 valsartan. Exercise appropriate care when initiating or ending concomitant treatment with such medicines.

Others:

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

As **VALGEN** is not metabolised to a significant extent, clinically relevant 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.

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 medicines that inhibit the renin-angiotensin- aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age should ensure effective contraception.

VALGEN acts directly on the RAAS and therefore should not be used in women planning to become pregnant. Healthcare providers prescribing **VALGEN** should counsel women of childbearing potential about the potential risk during pregnancy.

Pregnancy

When pregnancy is detected, **VALGEN** should be discontinued as soon as possible. Not to be used in pregnancy as teratogenicity has been shown in experimental animals.

Safety in pregnancy and lactation has not been established (see section 4.3).

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

Infants whose mothers have taken **VALGEN** 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.

Breastfeeding

It is not known whether valsartan is excreted in human milk. Since valsartan was excreted in the milk of lactating rats, mothers taking **VALGEN** should not breastfeed their infants.

Fertility

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

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60 kg patient).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Viral infections
	Less frequent	Upper respiratory tract infection, pharyngitis, sinusitis, rhinitis
Blood and the lymphatic system disorders	Frequency unknown	Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia
Immune system disorders	Frequency unknown	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	Less frequent	Hyperkalaemia
	Frequency unknown	Increase of serum potassium, hyponatraemia
Psychiatric disorders	Less frequent	Insomnia, decreased libido

Nervous system disorders	Frequent	Postural dizziness, dizziness
	Less frequent	Syncope, headache
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Cardiac failure
Vascular disorders	Frequent	Hypotension, orthostatic hypotension
	Frequency unknown	Vasculitis
Respiratory, thoracic and mediastinal disorders	Less frequent	Cough
Gastrointestinal disorders	Less frequent	Abdominal pain, diarrhoea, nausea
Hepatobiliary disorders	Frequency unknown	Elevation of liver function values including increase of serum bilirubin
	Less frequent	Angioedema

Skin and subcutaneous tissue disorders	Frequency unknown	Dermatitis bullous, rash, pruritus
Musculoskeletal and connective tissue disorders	Less frequent	Back pain
	Frequency unknown	Myalgia, arthralgia
Renal and urinary disorders	Frequent	Renal failure and impairment
	Less frequent	Acute renal failure, elevation of serum creatinine
	Frequency unknown	Serum urea increased
General disorders and administration site conditions	Less frequent	Fatigue, asthenia
	Frequency unknown	Oedema

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. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

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

Treatment

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms; stabilisation of the circulatory condition is of prime importance. If the ingestion is recent, vomiting should be induced if the patient is conscious. If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken. Otherwise, the usual treatment would be intravenous infusion of normal saline.

VALGEN is unlikely to be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonists, plain.

ATC code: C09CA03

Pharmacological classification: A7.1.3 Vascular medicines – other hypotensives

Valsartan is an orally active, specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the angiotensin 1 (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 greater affinity (about 20 000 fold) for the AT_1 receptor than for the AT_2 receptor.

The angiotensin 2 (AT_2) 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. 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 treatment.

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

Post-myocardial infarction:

A study in patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction (baseline treatment included acetylsalicylic acid, beta-blockers, ACE inhibitors, thrombolytics and statins) indicated:

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

Valsartan was 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 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 h 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 to 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 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 multi-exponential decay kinetics (t½ α < 1 h and t½ β about 9 h). 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 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

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.

Special Populations:

Elderly:

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.

Impaired Renal Function:

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).

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 to 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Povidone K-30

Silica, colloidal anhydrous

Tablet coating

Hypromellose

Titanium dioxide

Macrogol / PEG 8000

Iron oxide yellow

Iron oxide black [40, 160 and 320 mg tablets]

Iron oxide red [80, 160 and 320 mg tablets]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ˚C in a dry place.

Protect from moisture.

Keep container tightly closed.

Keep blister in the carton until required for use.

6.5 Nature and contents of container

28’s or 30’s HDPE bottle packs or cold form blister packs.

HDPE bottle pack comprising of white HDPE bottle with white opaque polypropylene closure with induction sealing liner. The HDPE bottle pack may either be placed in an outer cardboard carton or provided without a carton, based on commercial requirement. In case the HDPE bottle pack is not supplied in an outer carton, the leaflet shall be placed as an outsert.

Cold form blister pack comprising of cold form laminate (aluminium foil laminated to oriented polyamide on one side and to PVC on the other side i.e. OPA/Al/PVC) on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Suitable number of blister strips will be placed in an outer cardboard carton. The number of tablets per strip and the number of strips in each carton shall be based on commercial requirement.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1601

Republic of South Africa

8 REGISTRATION NUMBERS

VALGEN 40 mg: 47/7.1.3/1255

VALGEN 80 mg: 47/7.1.3/1256

VALGEN 160 mg: 47/7.1.3/1257

VALGEN 320 mg: 47/7.1.3/1258

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 February 2022

10 DATE OF REVISION OF THE TEXT

03 December 2024