PROFESSIONAL INFORMATION

REGOVAL RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

REGOVAL 40 mg film coated tablets

REGOVAL 80 mg film coated tablets

REGOVAL 160 mg film coated tablets

REGOVAL 320 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

REGOVAL 40 mg tablets contain sorbitol 4,6 mg and sugar (lactose monohydrate) 0,5 mg per tablet.

REGOVAL 80 mg tablets contain sorbitol 9,3 mg and sugar (lactose monohydrate) 1,1 mg per tablet.

REGOVAL160 mg tablets contain sorbitol 18,5 mg and sugar (lactose monohydrate) 2,2 mg per tablet.

REGOVAL 320 mg tablets contain sorbitol 37 mg and sugar (lactose monohydrate) 4,3 mg per tablet.

REGOVAL is essentially sodium free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

REGOVAL 40 mg: Cylindrical, biconvex, scored on one side, yellow, film coated tablets.

REGOVAL 80 mg: Cylindrical, scored on one side, pink, film coated tablets.

REGOVAL 160 mg: Cylindrical, biconvex, scored on one side, ochre, film coated tablets.

REGOVAL 320 mg: Oblong, scored on one side, greyish-violet, film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Treatment of mild to moderate 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

REGOVAL 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 REGOVAL 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.

REGOVAL 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, REGOVAL 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 3 months, based on the patient's tolerability to REGOVAL during titration. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction.

REGOVAL 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 REGOVAL 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

NOTE for all indications: No dosage adjustment is required for patients with mild to moderate renal impairment (where creatinine clearance, CrCl, is 30 to < 90 mL/min). A lower dose should be considered for patients with a history of hepatic impairment (see section 4.4).

Paediatric population

Use in children and adolescents

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

Method of administration

Oral use.

REGOVAL is given orally with or without food.

Missed dose:

Doctors should advise patients who forget to take REGOVAL to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- known hypersensitivity to valsartan or to any of the excipients of REGOVAL (see section 6.1)
- 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)
- severe renal function impairment (CrCl < 30 mL/min)
- bilateral renal artery stenosis
- renal artery stenosis in patients with a single kidney
- aortic stenosis
- mitral valve stenosis
- concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.4)
- concomitant use of fluoroquinolones with ACE inhibitors/ARBs is contraindicated in patients with moderate to severe renal impairment (CrCl < 30 mL/min) and in elderly patients
- porphyria
- lithium therapy: Concomitant administration with REGOVAL may lead to toxic blood concentrations of lithium section 4.5)
- pregnancy and lactation (see section 4.6)
- the concomitant use of REGOVAL with aliskiren-containing medicines in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1,73 m^2) is contraindicated (see sections 4.4 and 4.5)

- concomitant use of REGOVAL with aliskiren in patients with Type 2 diabetes mellitus (see section 4.5, subsection dual blockade of the RAAS).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving REGOVAL, 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 CrCl > 30 to ≤ 90 mL/min) or for patients with hepatic insufficiency of non-biliary origin and without cholestasis.

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

The concomitant use of ARBs – including valsartan – or of ACE inhibitors 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

No dosage adjustment is required for patients with hepatic insufficiency. Valsartan is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower REGOVAL clearance (see section 5.2). Particular caution should be exercised when administering REGOVAL 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 therapy with REGOVAL.

Sodium and/or volume depletion should be corrected before starting treatment with REGOVAL, 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 REGOVAL has not been established and should therefore not be prescribed to these patients (see section 4.3).

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 bilateral or unilateral renal artery stenosis, therefore, monitoring of renal function is recommended when patients are treated with REGOVAL.

Kidney transplantation

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

Primary hyperaldosteronism

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

REGOVAL 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 REGOVAL, 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 REGOVAL 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 REGOVAL is used in combination with an ACE inhibitor. In patients with heart failure, caution should be observed with concurrent administration of ACE inhibitors, beta-blockers, and REGOVAL as an increase in mortality has been reported on this triple therapy.

Triple combination of an ACE inhibitor, a mineralocorticoid receptor antagonist and valsartan, as in REGOVAL, 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 REGOVAL 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 REGOVAL 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.

REGOVAL 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)

Caution is required while co-administering ARBs, including REGOVAL, with other medicines blocking the RAAS such as ACE inhibitors or aliskiren (see section 4.5 and 4.3).

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

Concomitant use of fluoroquinolones and ACE inhibitors/ARBs may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment (CrCl <30 mL/min) and elderly patients (see section 4.3).

Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/ARBs whether used separately and/or concomitantly.

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

Lactose intolerance

REGOVAL contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take REGOVAL.

Sodium

REGOVAL contains up to 1,25 mg sodium per 320 mg tablet, 0,63 mg per 160 mg tablet, 0,31 mg per 80 mg tablet and 0,16 mg per 40 mg tablet. Thus, this medicine contains less than 1 mmol sodium (23 mg) per dose, and is essentially ‘sodium-free’.

Paediatric population

Impaired Renal function

Use in paediatric patients with a CrCl < 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, REGOVAL 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 REGOVAL 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 ARBS, ACE inhibitors, or aliskiren**:***

Clinical trial data has shown that dual blockade of the 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 (see sections 4.3, 4.4 and 5.1). It is recommended to monitor blood pressure, renal function and electrolytes in patients on REGOVAL and other medicines that affect the RAAS (see section 4.4).

Concomitant use of angiotensin receptor antagonists (ARBs) including REGOVAL with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min) (see section 4.4).

The concomitant use of REGOVAL 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 (ARBs):

Concomitant use of fluoroquinolones and ACE inhibitors/ARBs 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).

Concomitant use not recommended

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 contraindicated (see section 4.3). Monitoring of lithium levels is therefore recommended, if needed.

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

Concomitant therapy with potassium sparing diuretics, such as spironolactone, triamterene and amiloride, potassium supplements or salt substitutes containing potassium that may lead to increases in potassium, and in patients with heart failure to increase in serum creatinine, are contraindicated (see sections 4.3 and 4.4). If needed, serum potassium is to be monitored.

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 in patients who are elderly, volume-depleted (including those on diuretic therapy), or who have compromised renal function. Therefore, monitoring of renal function at the beginning of the treatment and when adjusting the dose is recommended in those patients taking REGOVAL and NSAIDs concomitantly. Adequate hydration of the patient is also recommended.

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, glibenclamide.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential /contraception in males and females

Women of childbearing age should ensure effective contraception.

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

Pregnancy

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

In case of accidental exposure to ARB therapy, appropriate foetal monitoring should be considered. Infants whose mothers have taken REGOVAL 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

Because no information is available regarding the use of valsartan during breastfeeding, REGOVAL is contraindicated during lactation (see section 4.3). Alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

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 60kg 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 REGOVAL.

4.8 Undesirable effects

Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Frequent Less frequent	Viral infections Upper respiratory tract infection, pharyngitis, sinusitis, rhinitis
Blood and 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 Frequency unknown	Hyperkalaemia Increase of serum potassium*, hyponatraemia
Psychiatric disorders	Less frequent	Insomnia, decreased libido
Nervous system disorders	Frequent Less frequent Frequency unknown	Postural dizziness Syncope, dizziness Headache
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Cardiac failure
Vascular disorders	Frequent Frequency unknown	Hypotension, orthostatic hypotension 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*
Skin and subcutaneous tissue disorders	Frequency unknown	Angioedema, rash*, pruritus*, dermatitis bullous*

Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Back pain Myalgia*, arthralgia
Renal and urinary disorders	Frequent Less frequent Frequency unknown	Renal failure and impairment Acute renal failure, elevation of serum creatinine Serum urea increased*
General disorders and administrative site conditions	Less frequent	Fatigue, asthenia, oedema

*Post-marketing

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse to SAHPRA via the online service for adverse drug reaction reporting by using either of the following links: https://www.sahpra.org.za/Publications/Index/8 or https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/ .

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms

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

Management of overdose

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 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.

REGOVAL is unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: C09CA03

Pharmacological classification: A7.1.3 Vascular medicines – other hypotensives.

Mechanism of action

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.

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

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 - 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.

Post-myocardial infarction

The “VALsartan In Acute myocardial iNfarcTion trial” (VALIANT) was a randomized, controlled, multinational, double-blind study in 14 703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricular systolic dysfunction.

Patients were randomized after the onset of myocardial infarction symptoms to one of three treatment groups: valsartan was up-titrated from 20 mg twice daily to highest tolerated dose up to a maximum of 160 mg twice daily.

Baseline therapy included acetylsalicylic acid (91 %), beta-blockers (70 %), ACE inhibitors (40 %), thrombolytics (35 %), and statins (34 %).

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 is low (about 17 L), indicating that valsartan is not extensively distributed into tissues.

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 half-life of valsartan is 6 hours.

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.

Linearity/non-linearity

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.

Pharmacokinetics in special patient groups

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 - 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 - 16 years and similar to that of adults receiving the same formulation (see section 4.2 and 4.3).

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Colloidal anhydrous silica

Crospovidone

Magnesium carbonate

Microcrystalline cellulose

Povidone

Pregelatinised starch

Pregelatinised maize starch

Sodium lauryl sulphate

Sodium stearyl fumarate

Sorbitol.

Film coating

Hypromellose

Indigo carmine aluminium lake (320 mg tablets)

Iron oxide brown (160 mg & 320 mg tablets)

Iron oxide red (80 mg & 320 mg tablets)

Iron oxide yellow (40 mg & 160 mg tablets)

Lactose monohydrate

Macrogol

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

REGOVAL 320 mg: 36 months

REGOVAL 40 mg, REGOVAL 80 mg & REGOVAL 160 mg: 24 months

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from moisture.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

The tablets are packaged in PVC-PE- PVDC (triplex)/aluminium blister packs of thirty (30) tablets placed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, 7945

Cape Town, South Africa

8. REGISTRATION NUMBER(S)

REGOVAL 40 mg: A43/7.1.3/0547*

REGOVAL 80 mg: A43/7.1.3/0548

REGOVAL 160 mg: A43/7.1.3/0549

REGOVAL 320 mg: A47/7.1.3/0693

*Not all strengths are marketed

9. DATE OF FIRST AUTHORISATION

REGOVAL 320 mg: 19 October 2021

REGOVAL 40 mg, REGOVAL 80 mg & REGOVAL 160 mg: 21 April 2016

10. DATE OF REVISION OF THE TEXT

08 November 2023

NAMIBIA:

REGOVAL 80 mg: NS2 22/7.1.3/0035

REGOVAL 160 mg: NS2 22.7.1.3/0036