PROFESSIONAL INFORMATION (APPROVED)

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

REGOVAL CO 80/12,5 mg, film coated tablets

REGOVAL CO 160/12,5 mg, film coated tablets

REGOVAL CO 160/25 mg, film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REGOVAL CO 80/12,5 mg: Each film coated tablet contains 80 mg valsartan and 12,5 mg hydrochlorothiazide.

REGOVAL CO 160/12,5 mg: Each film coated tablet contains 160 mg valsartan and 12,5 mg hydrochlorothiazide.

REGOVAL CO 160/25 mg: Each film coated tablet contains 160 mg valsartan and 25 mg hydrochlorothiazide.

REGOVAL CO contains sorbitol (9,25 mg in a 80/12,5 mg tablet and 18,5 mg in each 160/12,5 and 160/25 mg tablet) and sugar (lactose monohydrate) (1,06 mg in a 80/12,5 mg tablet and 2,12 mg in 160/12,5 and 160/25 mg tablets) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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Film-coated tablets.

REGOVAL CO 80/12,5 mg: Cylindrical, biconvex, pink film coated tablets.

REGOVAL CO 160/12,5 mg: Cylindrical, biconvex, reddish film coated tablets.

REGOVAL CO 160/25 mg: Cylindrical, biconvex, brown film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of mild to moderate hypertension.
- REGOVAL CO is indicated for the treatment of hypertension in patients whose blood pressure has been stabilised at the same dosages of the individual components given together.

4.2 Posology and method of administration

The recommended dose of REGOVAL CO is 1 tablet per day.

When clinically appropriate either REGOVAL CO 80/12,5 mg or REGOVAL CO 160/12,5 mg may be used.

If necessary, REGOVAL CO 160/25 mg may be used.

The maximum antihypertensive effect is seen within 2 - 4 weeks.

For initial therapy, the usual starting dose is 160/12,5 mg once daily, the dosage can be increased after 1-2 weeks of therapy to a maximum of 320/25 mg once daily as needed to control blood pressure.

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REGOVAL-CO is not recommended as initial therapy in patients with intravascular volume depletion (see section 4.4).

The maximum daily dose is 320/25 mg.

Special populations

Hepatic insufficiency:

No dosage adjustment is required in patients with mild to moderate hepatic insufficiency of non-biliary origin and without cholestasis.

REGOVAL CO is contraindicated in patients with severe hepatic impairment or with biliary cirrhosis and cholestasis (see section 4.3).

Renal impairment:

No dose adjustment is required for patients with mild to moderate renal impairment (Glomerular Filtration Rate (GFR) ≥ 30 mL/min). Due to the hydrochlorothiazide component, REGOVAL CO is contraindicated in patients with severe renal impairment and those with anuria (see section 4.3).

Paediatric population

The safety and efficacy of REGOVAL CO have not been established in children.

Method of administration

Oral use.

REGOVAL CO can be taken with or without food and should be administered with water.

Missed dose

Doctors should advise patients who forget to take REGOVAL CO 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

- Hypersensitivity to valsartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the ingredients of REGOVAL CO.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs). Such 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) or anuria.
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant use of fluoroquinolones with ACE inhibitors/ARBs is contraindicated in patients with moderate to severe renal function impairment (creatinine clearance

less than 30 mL/min) and in elderly patients.

- Concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride.
- Lithium therapy: Concomitant administration with REGOVAL CO may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see sections 4.4 and 4.6).
- The concomitant use of REGOVAL CO with renin inhibitors such as aliskiren is contraindicated (see sections 4.4 and 4.5).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- REGOVAL CO is contraindicated in patients with Addison's disease due to the hydrochlorothiazide component.
- Patients with primary hyperaldosteronism should not be treated with REGOVAL CO as their renin-angiotensin system is not activated (see section 4.4).
- Porphyria.

4.4 Special warnings and precautions for use

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

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Sodium and/or volume-depleted patients:

- 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 REGOVAL CO. Sodium and/or volume-depletion should be corrected before starting treatment with REGOVAL CO, for example, by reducing the diuretic dose (see section 4.2).
- Symptomatic hypotension may occur after initiation of REGOVAL CO. If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment with REGOVAL CO may be continued once blood pressure has stabilised.

***Serum electrolyte changes*:**

- Concomitant use with potassium supplements, salt substitutes containing potassium or other medicines that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium**.** Frequent monitoring of serum potassium is recommended (see section 4.5).
- Concomitant use with potassium-sparing diuretics is contraindicated (see section 4.3).
- Hydrochlorothiazide, as contained in REGOVAL CO, has been linked to hypochloraemic alkalosis and hyponatraemia, or the exacerbation of pre-existing hyponatraemia.
- Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in isolated cases. Regular monitoring of serum sodium concentrations is recommended.

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- The urinary excretion of magnesium may be increased by hydrochlorothiazide, as contained in REGOVAL CO, which could result in hypomagnesaemia (see section 4.5).
- Hypomagnesaemia or hypokalaemia, induced by hydrochlorothiazide, as contained in REGOVAL CO, may occur as unwanted effects, favouring the onset of digoxin-induced cardiac dysrhythmias.
- If hypokalaemia is accompanied by clinical signs (e.g., muscular weakness, paresis, or ECG alterations), REGOVAL CO should be discontinued. Correction of hypokalaemia and any hypomagnesemia is recommended prior to the initiation of thiazides. Frequent monitoring is recommended.
- Decreased urinary calcium excretion caused by hydrochlorothiazide, as contained in REGOVAL CO, may result in an intermittent and slightly raised serum calcium concentration. Should marked hypercalcaemia occur, it may be evidence of underlying hyperparathyroidism. REGOVAL CO therapy should be discontinued before carrying out tests for parathyroid function (see section 4.5).

Other metabolic disturbances:

- Hydrochlorothiazide, as contained in REGOVAL CO, may increase serum levels of uric acid (either causing or exacerbating hyperuricemia and precipitating gout in susceptible patients), triglyceride and cholesterol, as well as changes in glucose tolerance. In diabetic patients, dosage adjustments of insulin or oral hypoglycaemic medicines may be required (see section 4.5).

Impaired renal function:

- Concomitant use of fluoroquinolones with ACE inhibitors/ ARBs may precipitate

acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors /ARBs, whether used separately and/or in combination.

- No dosage adjustment is required for patients with mild renal impairment (creatinine clearance > 70 mL/min). However, in moderate to severe cases (creatinine clearance < 70 mL/min) insufficient data are available. REGOVAL CO should not be used because of increased side effects (see section 4.3).
- REGOVAL CO is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.3).

Hepatic impairment:

- Reduced doses must be considered in patients with hepatic impairment.
- Valsartan is mostly eliminated unchanged in the bile, and patients with biliary obstructive disorders showed lower valsartan clearance (see section 5.2). REGOVAL CO should not be used in patients with biliary obstructive disorders.

Post-myocardial infarction/heart failure:

- Use of REGOVAL CO in patients with post-myocardial infarction or heart failure, commonly results in some reduction in blood pressure, but discontinuation of REGOVAL CO 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.

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- As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the RAAS, treatment with ACE inhibitors such as valsartan 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 post-myocardial infarction and heart failure should always include assessment of renal function.
- In patients with heart failure, caution should be observed with concurrent administration of ACE inhibitors, beta-blockers and REGOVAL CO, as an increase in mortality has been reported on this triple therapy.

Dehydration:

- A reduction in salt or fluid volume may increase the risk of symptomatic hypotension. Sodium and or volume-depletion may be caused by excessive perspiration, vomiting, diarrhoea, prolonged diuretic therapy, dialysis or dietary salt restriction. Caution is advised when exercising or during hot weather, because of the risk of dehydration (due to excessive sweating) which may result in hypotension.

Systemic lupus erythematosus:

- Exacerbation or activation of systemic lupus erythematosus has been reported with the use of hydrochlorothiazide, as contained in REGOVAL CO.

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 renin inhibitors such as aliskiren may increase the risk

of hypotension, hyperkalaemia and decrease renal function (including acute renal failure). Dual blockade of RAAS through the combined use of REGOVAL CO and renin inhibitors such as aliskiren is therefore contraindicated (see section 4.3). REGOVAL CO should not be used concomitantly with aliskiren (see section 4.3).

Primary hyperaldosteronism:

- Patients with primary hyperaldosteronism should not be treated with REGOVAL CO as their renin-angiotensin system is not activated (see section 4.3).

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 CO should be discontinued immediately in patients who develop angioedema and should not be re-administered (see sections 4.3 and 4.8).

Photosensitivity:

- Cases of photosensitivity reactions have been reported with hydrochlorothiazide diuretics (see section 4.8). If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of REGOVAL CO is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma:

- Hydrochlorothiazide, a sulfonamide, as contained in REGOVAL CO has been associated with an idiosyncratic reaction resulting in acute transient myopia and

acute angle-closure glaucoma.

Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to a week of initiation.

- Untreated acute-angle closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue REGOVAL CO as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Renal artery stenosis:

- REGOVAL CO should not be used to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, since blood urea and serum creatinine may increase in such patients (see section 4.3).

Kidney transplantation:

- There is currently no experience on the safe use of REGOVAL CO in patients who have recently undergone kidney transplantation (see section 4.3).

Non-melanoma skin cancer:

- An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies. Photosensitising actions of HCTZ could act as a possible mechanism for NMSC.

  Patients taking REGOVAL CO should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any

suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies.

REGOVAL CO should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

General:

- Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Information on excipients of REGOVAL CO

Lactose:

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

REGOVAL CO contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Sorbitol:

Patients with the rare hereditary condition of sorbitol intolerance should not take REGOVAL CO.

Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

4.5 Interaction with other medicines and other forms of interaction

Contraindication of concomitant use (see section 4.3):

Lithium:

Increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and hydrochlorothiazide (see section 4.3).

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).

Potassium-sparing diuretics:

Concomitant use with potassium-sparing diuretics (e.g., spironolactone, triamterene and amiloride), potassium supplements, salt substitutes containing potassium or other medicines that may alter potassium levels (e.g., heparin) may lead to increases in serum potassium.

REGOVAL CO and potassium-sparing diuretics should not be given together (see sections 4.3 and 4.4).

Concomitant use not recommended (see section 4.4):

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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 REGOVAL CO. Exercise appropriate care when initiating or ending concomitant treatment with such medicines.

Concomitant use requiring caution:

Other antihypertensive medicines:

The antihypertensive effects of REGOVAL CO may be potentiated by other medicines that lower blood pressure (e.g., guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs and Direct Renin Inhibitors (DRIs)).

Pressor amines:

Pressor amines [e.g., epinephrine (adrenaline)] – hydrochlorothiazide, as contained in REGOVAL CO, may decrease response to pressor amines. This decrease in response is not sufficient to preclude the use of pressor amines.

(NSAIDs) including selective COX-2 inhibitors, aspirin (acetylsalicylic acid) (> 3 g/day), and non-selective NSAIDs:

The diuretic and anti-hypertensive activity of the hydrochlorothiazide component of REGOVAL CO may weaken with concomitant administration of non-steroidal anti-inflammatory drugs (NSAIDs) including selective COX-2 inhibitors, aspirin (acetylsalicylic

acid) (> 3 g/day), and non-selective NSAIDs (e.g., indomethacin, salicylic acid derivative). Acute renal failure may be induced by concurrent hypovolaemia. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Interactions related to valsartan:

Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren:

Clinical trial data have 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 and 4.4).

No interaction:

Under monotherapy with valsartan, no drug interactions of clinical significance have been found with the following drugs: cimetidine, warfarin, furosemide, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

Interactions related to hydrochlorothiazide:

Medicines affecting serum potassium levels:

Concomitant use of corticosteroids, kaliuretic diuretics, carbenoxolone, amphotericin, ACTH, salicylic acid derivatives, laxatives, or penicillin G, with hydrochlorothiazide, as contained in REGOVAL CO, may intensify electrolyte depletion and hypokalaemia.

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If these medicines are to be prescribed with REGOVAL CO, monitoring of potassium plasma levels is advised (see section 4.4).

Medicines that could induce torsade's de pointes:

Due to the risk of hypokalaemia, REGOVAL CO should be administered with caution when associated with medicines that could induce torsade's de pointes, in particular Class Ia and Class III antidysrhythmics (disopyramide, procainamide, quinidine and sotalol) and some antipsychotics (haloperidol, thioridazine and pimozide).

Medicines affecting serum sodium levels:

The hyponatremic effect of diuretics may be intensified by concomitant administration of medicines such as anti-depressant, antipsychotics, antiepileptics, etc. Caution is advised in long term administration of these medicines (see section 4.4).

Digitalis glycosides:

Thiazide-induced hypokalaemia or hypomagnesaemia may

occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias.

Calcium salts and Vitamin D:

Administration of hydrochlorothiazide, as contained in REGOVAL CO, with calcium salts or Vitamin D may lead to a rise in serum calcium.

Antidiabetic medicine (oral medicines and insulin):

Hydrochlorothiazide may alter glucose tolerance. Dosage adjustment of the antidiabetic medicine may be required with the concomitant use of REGOVAL CO (see section 4.4). Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta blockers and diazoxide:

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Concomitant use of hydrochlorothiazide with beta blockers may increase the risk of hyperglycaemia. REGOVAL CO may enhance the hyperglycaemic effect of diazoxide.

Anticholinergic medicines and other medicines affecting gastric motility:

Anticholinergic medicines (e.g., biperiden, atropine) may increase the bioavailability of hydrochlorothiazide, as contained in REGOVAL CO, apparently due to a decrease in gastrointestinal motility and the stomach-emptying rate.

Conversely prokinetic drugs, such as cisapride, may decrease bioavailability of thiazide-type diuretics.

Methyldopa:

Haemolytic anaemia occurring with concurrent use of methyldopa and hydrochlorothiazide, as contained in REGOVAL CO, has been reported.

Cholestyramine and colestipol:

Cholestyramine and colestipol decreases the absorption of hydrochlorothiazide, as contained in REGOVAL CO. This could result in sub-therapeutic effects of hydrochlorothiazide. However, staggering the dosage of REGOVAL CO and resin such that hydrochlorothiazide is administered at least 4 hours before or 4 - 6 hours after the administration of resins would potentially minimise the interaction.

Ciclosporin:

Concurrent therapy with ciclosporin may increase the risk of gout-type complications and hyperuricaemia.

Iodine contrast media:

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

Co-administration of hydrochlorothiazide, as contained in REGOVAL CO, may:

- increase the risk of side effects caused by amantadine
- increase the incidence of hypersensitivity reactions to allopurinol
- add to the hyperglycaemic effect of diazoxide
- potentiate the action of skeletal muscle relaxants such as curare derivatives
- decrease the renal excretion of cytotoxic medicines (e.g., methotrexate, cyclophosamide) and cause their myelosuppressive effects.

Alcohol, barbiturates or narcotics:

Potentiation of orthostatic hypotension caused by hydrochlorothiazide, as contained in REGOVAL CO, may occur.

Non depolarising muscle relaxants (e.g., tubocurarine)

Hydrochlorothiazide, as contained in REGOVAL CO, may increase the responsiveness to the muscle relaxant.

Since REGOVAL CO 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 REGOVAL CO.

4.6 Fertility, pregnancy and lactation

REGOVAL CO is contraindicated in pregnancy and lactation.

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

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should ensure effective contraception (see section 4.3).

Pregnancy

When pregnancy is planned or confirmed, REGOVAL CO should be discontinued.

Medicines affecting the renin-angiotensin system, such as REGOVAL CO, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

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

Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with foetal or neonatal jaundice or thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

Breastfeeding

Hydrochlorothiazide is excreted in breastmilk. Mothers on REGOVAL CO should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

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REGOVAL CO may affect the ability to drive and use machines. When driving vehicles or operating machines, patients should take into account that visual disorders, dizziness or weariness may occur during treatment of hypertension.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Valsartan:

System Organ Class	Frequency	Side effects
Infections and Infestations	Less frequent	Viral infections, upper respiratory tract infection, pharyngitis or sinusitis, rhinitis
Blood and lymphatic system disorders	Frequent Frequency unknown	Neutropenia Thrombocytopenia decrease in haemoglobin, decrease in haematocrit
Immune system disorders	Frequency unknown	Anaphylactic reactions including serum sickness, angioedema
Metabolism and nutrition disorders	Less frequent Frequency unknown	Hyperkalaemia Increase of serum potassium, hyponatraemia
Psychiatric disorders	Less frequent	Insomnia, decreased libido
Nervous system disorders	Less frequent	Syncope, headache, dizziness
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus

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Vascular disorders	Less frequent Frequency unknown	Postural hypotension, hypotension (may occur in patients with volume depletion) Vasculitis
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Cough Rhinitis
Gastrointestinal disorders	Less frequent	Diarrhoea, abdominal pain, nausea
Hepatobiliary disorders	Less frequent Frequency unknown	Hepatitis, raised liver enzyme values Abnormal liver function test
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Rash, pruritus, dermatitis bullous Urticaria, alopecia
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Back pain, arthralgia, asthenia Myalgia, rhabdomyolysis
Renal and urinary disorders	Less frequent	Renal impairment, renal failure
General disorders and administrative site conditions	Less frequent	Fatigue, oedema

Hydrochlorothiazide:

System Organ Class	**Frequency**	**Side effects**

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Neoplasms benign and malignant (including cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders	Less frequent Frequency unknown	Agranulocytosis, thrombocytopenia, leucopenia, haemolytic anaemia, bone marrow failure Aplastic anaemia
Immune system disorders	Less frequent	Anaphylactic reactions, hypersensitivity reactions
Endocrine disorders	Less frequent	Pancreatitis
Metabolism and nutrition disorders	Frequent Less frequent	Electrolyte imbalance including hyponatraemia, hypokalaemia, increased blood lipids (mainly at higher doses), hypomagnesaemia, hyperuricaemia Anorexia, hypercalcaemia, glycosuria and worsening of diabetic metabolic state, hypochloraemic alkalosis
Psychiatric disorders	Less frequent	Depression, sleep disturbances
Nervous system disorders	Less frequent Frequency unknown	Headache, dizziness, paraesthesia Restlessness, fever
Eye disorders	Less frequent Frequency unknown	Visual impairment Xanthopsia, transient blurred vision, acute angle-closure glaucoma

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Ear and labyrinth disorders	Frequency unknown	Vertigo
Cardiac disorders	Less frequent	Dysrhythmias
Vascular disorders	Frequent Frequency unknown	Postural hypotension, orthostatic hypotension which may be aggravated by alcohol, anaesthetics or sedatives Necrotising angitis (vasculitis) (cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory distress including pneumonitis and pulmonary oedema
Gastrointestinal disorders	Frequent Less frequent	Loss of appetite, nausea, vomiting Gastric irritation, anorexia, constipation, diarrhoea, sialadenitis
Hepatobiliary disorders	Less frequent	Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Urticaria, other forms of rash Photosensitivity Purpura, Stevens-Johnson syndrome, necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, erythema multiforme, pseudoporphyria
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Muscle spasm

Renal and urinary disorders	Frequency unknown	Renal failure, renal dysfunction, interstitial nephritis
Reproductive system and breast disorders	Frequent	Impotence
General disorders and administrative site conditions	Frequency unknown	Pyrexia, asthenia

Valsartan and Hydrochlorothiazide:

The following additional adverse reactions have been reported with valsartan - hydrochlorothiazide combination:

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequency unknown	Neutropenia
Metabolism and nutrition disorders	Frequent Frequency unknown	Dehydration Hypokalaemia, hyponatraemia
Nervous system disorders	Less frequent Frequency unknown	Dizziness, paraesthesia Syncope
Eye disorders	Less frequent	Blurred vision
Ear and labyrinth disorders	Less frequent	Tinnitus
Vascular disorders	Less frequent	Hypotension

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Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Cough Non-cardiogenic pulmonary oedema, sinus and nasal congestion, upper respiratory tract infection
Gastrointestinal disorders	Less frequent	Diarrhoea
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, myalgia, sprains and strains
Renal and urinary disorders	Frequency unknown	Impaired renal function, renal failure
General disorders and administrative site conditions	Less frequent	Fatigue
Investigations	Frequency unknown	Increased serum uric acid, increased serum bilirubin and serum creatinine, elevation of blood urea

The following events have also been observed during clinical trials:

Abdominal pain, upper abdominal pain, anxiety, arthritis, asthenia, back pain, bronchitis, acute bronchitis, chest pain, postural dizziness, dyspepsia, dyspnoea, dry mouth, epistaxis, erectile dysfunction, gastroenteritis, headache, hyperhidrosis, hypoesthesis, influenza, insomnia, ligament sprain, muscle spasms, muscle strain, nasal congestion, nasopharyngitis, nausea, neck pain, oedema, peripheral oedema, otitis media, pain in extremity, palpitations, pharyngolaryngal pain, pollakiuria, pyrexia, rash, sinusitis, situs congestion, somnolence tachycardia, upper respiratory tract infections, urinary tract infections, vertigo, viral infections, vision disturbance.

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Post-marketing data revealed angioneurotic oedema, rash, pruritus, and other hypersensitivity/ allergic reactions including serum sickness, and vasculitis.

Cases of renal impairment and myalgia have also been reported.

There have also been reported cases of hydrochlorothiazide-induced pulmonary oedema with granulocytic infiltration and lgG deposition in alveolar membranes. Non-cardiogenic pulmonary oedema may be an immunologically mediated idiosyncratic reaction to hydrochlorothiazide.

Description of selected adverse reactions

Non-melanoma skin cancer: based on available data from epidemiological studies, cumulative dose dependent association between hydrochlorothiazide and NMSC has been observed (see also sections 4.4 and 5.1).

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

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

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4.9 Overdose

In overdose, side effects will be exacerbated and exaggerated (see section 4.8).

Signs and symptoms:

Valsartan:

Overdose with valsartan, as contained in REGOVAL CO, may result in marked hypotension, which could lead to a depressed level of consciousness, circulatory collapse and/or shock. Bradycardia or tachycardia may also occur with REGOVAL CO overdose.

Hydrochlorothiazide:

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digoxin has also been administered, hypokalaemia may accentuate cardiac dysrhythmias.

Management of overdose

Valsartan:

If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be intravenous infusion of normal saline solution.

Hydrochlorothiazide:

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

PROFESSIONAL INFORMATION (APPROVED)

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II receptor antagonists and diuretics, valsartan and diuretics.

ATC code: C09D A03

Pharmacological classification: A 7.1.3 Other hypotensives.

Mechanism of action

Valsartan:

Valsartan is a 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. 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.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak action is achieved within 4 - 6 hours. The effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure is generally attained within 2 - 4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, an additional reduction in blood pressure is achieved.

PROFESSIONAL INFORMATION (APPROVED)

Hydrochlorothiazide:

Hydrochlorothiazide is a thiazide diuretic and antihypertensive medicine. It affects the distal renal tubular mechanism of electrolyte re-absorption and increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

5.2 Pharmacokinetic properties

Valsartan:

Absorption:

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

Food decreases exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (C_{max}) by about 50 %, although from about 8 hours post dosing, plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Biotransformation:

Steady-state volume of distribution is low (about 17 L).

Valsartan is highly bound to serum protein (94 - 97 %), mainly serum albumin. Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h). Valsartan is cleared from the circulation by the liver (about 70 % of total clearance).

PROFESSIONAL INFORMATION (APPROVED)

Elimination:

The terminal elimination half-life is about 5 - 9 hours. Following an oral dose, about 83 % is excreted in the faeces and 13 % in urine.

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 were observed to be similar in males and females.

Hydrochlorothiazide:

Absorption:

After oral administration of hydrochlorothiazide, absorption is rapid (t_{max} about 2 hours). After oral administration, the absolute bioavailability of hydrochlorothiazide is 60 - 80 %.
The increase in mean AUC is linear and dose proportional in the therapeutic range.
In the therapeutic range, the increase in mean AUC is linear and dose proportional. On repeated dosing, the kinetics of hydrochlorothiazide remain unchanged, and accumulation is minimal when dosed once daily.
Food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide. These changes, however, have little clinical importance and therefore hydrochlorothiazide can be given either with or without food.

Biotransformation:

The apparent volume of distribution is 4 – 8 L/kg.

Circulating hydrochlorothiazide is bound to serum proteins (40 – 70 %), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Elimination:

Hydrochlorothiazide is eliminated predominantly as unchanged medicine.

The plasma half-life of hydrochlorothiazide can vary between 6 - 15 hours in the terminal elimination phase. In the therapeutic range, the increase in mean AUC is linear and dose proportional.

Less than 95 % of the absorbed dose is eliminated unchanged in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Valsartan/Hydrochlorothiazide:

When co-administered with valsartan, the systemic availability of hydrochlorothiazide is reduced by about 30 %. The kinetics of valsartan are not noticeably affected when co-administered with hydrochlorothiazide. This interaction has no impact on the concurrent use of valsartan and hydrochlorothiazide.

Pharmacokinetics in special patient groups

Elderly:

AUC and elimination half-life of valsartan increase by 70 % and 35 %, respectively, when compared with those in younger patients. When compared to younger patients, limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both hypertensive and healthy elderly patients.

PROFESSIONAL INFORMATION (APPROVED)

Impaired Renal Function:

No data are available for patients undergoing dialysis, in patients with mild renal impairment (creatinine clearance > 70 mL/min) and in patients with moderate to severe renal impairment (creatinine clearance < 70 mL/min).

Valsartan/hydrochlorothiazide is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.3).

Valsartan is highly bound to plasma protein and is not removed by dialysis; however, clearance of hydrochlorothiazide will be achieved by dialysis.

The renal clearance of hydrochlorothiazide consists of passive filtration and active secretion into the renal tubule. Since hydrochlorothiazide is cleared almost exclusively via the kidneys, renal function has a significant effect on the kinetics of hydrochlorothiazide (see section 4.3).

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 mild to moderate hepatic insufficiency of non-biliary origin and without cholestasis. The AUC for valsartan has been observed to be approximately double in patients with biliary cirrhosis or biliary obstruction (see section 4.4).

The pharmacokinetics of hydrochlorothiazide are not notably affected by hepatic disease.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cores:

Colloidal anhydrous silica

Colloidal silicon dioxide

Crospovidone

Magnesium carbonate

Microcrystalline cellulose

Pregelatinised starch

Povidone

Sodium lauryl sulphate

Sodium stearyl fumarate

Sorbitol powder

Coating:

Hypromellose

Lactose monohydrate

Macrogol 4000

Opadry white

Titanium dioxide

PROFESSIONAL INFORMATION (APPROVED)

Colouring:

Iron oxide brown (160/12,5 mg and 160/25 mg tablets)

Iron oxide red (80/12,5 mg and 160/12,5 mg tablets)

Iron oxide yellow (160/25 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.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

REGOVAL CO tablets are available in clear PVC/PE/PVDC / aluminium blister strips.

Pack sizes of 14, 28, 30, 56, 98 or 280 tablets in blister strips of 7, 10 or 15’s are packed in a printed outer carton.

6.6 Special precautions for disposal

No special requirements.

PROFESSIONAL INFORMATION (APPROVED)

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

REGOVAL CO 80/12,5 mg: A44/7.1.3/0018

REGOVAL CO 160/12,5 mg: A44/7.1.3/0019

REGOVAL CO 160/25 mg: A44/7.1.3/0020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 2013

10. DATE OF REVISION OF THE TEXT

11 October 2023

NAMIBIA:

REGOVAL CO 80/12,5 mg: NS2 14/7.1.3/0061

REGOVAL CO 160/12,5 mg: NS2 14/7.1.3/0062

REGOVAL CO 160/25 mg: NS2 14/7.1.3/0063

PROFESSIONAL INFORMATION (APPROVED)

MOZAMBIQUE:

REGOVAL CO 80/12,5 mg: 4817

REGOVAL CO 160/12,5 mg: 4818

REGOVAL CO 160/25 mg: 4819

ZIMBABWE:

REGOVAL CO 80/12,5 mg: P.P.10 2017/12.3.5/5416

REGOVAL CO 160/12,5 mg: P.P.10 2017/12.3.5/5417

REGOVAL CO 160/25 mg: P.P.10 2017/12.3.5/5418