REGDUAL CO

SCHEDULING STATUS S5

1. NAME OF THE MEDICINE
REGDUAL CO 80/12.5 mg, film coated tablets
REGDUAL CO 160/12.5 mg film coated tablets
REGDUAL CO 160/25 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
REGDUAL CO 80/12.5 mg: Each film coated tablet contains 80 mg valsartan and 12.5 mg hydrochlorothiazide.
REGDUAL CO 160/12.5 mg: Each film coated tablet contains 160 mg valsartan and 12.5 mg hydrochlorothiazide.
REGDUAL CO 160/25 mg: Each film coated tablet contains 160 mg valsartan and 25 mg hydrochlorothiazide.
REGDUAL CO contains sorbitol (9.25 mg in 80/12.5 mg tablet and 18.5 mg in each 160/12.5 mg and 160/25 mg tablet) and sugar (sucrose monohydrate) (1.66 mg in 80/12.5 mg tablet and 2.12 mg in each 160/12.5 and 160/25 mg tablet) (see section 4.4).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablets.
REGDUAL CO 80/12.5 mg: Cylindrical, biconvex, pink film coated tablets.
REGDUAL CO 160/12.5 mg: Cylindrical, biconvex, reddish film coated tablets.
REGDUAL CO 160/25 mg: Cylindrical, biconvex, brown film coated tablets.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
- Treatment of mild to moderate hypertension.
- It is a fixed combination for patients in whom control of hypertension is patients whose blood pressure has been stabilised at the same dosages of the individual components given together.

4.2 Posology and method of administration
Posology
The recommended dose of REGDUAL CO is 1 tablet per day.
When clinically appropriate either REGDUAL CO 80/12.5 mg or REGDUAL CO 160/12.5 mg may be used.
If necessary, REGDUAL CO 160/25 mg may be used.
The maximum dosage of REGDUAL CO is one tablet daily.
For initial therapy, the usual starting dose is 160/12.5 mg once daily, the dosage can be increased to 160/25 mg once daily if necessary. Titrating to a maximum of 320/25 mg once daily is a logical second step.
REGDUAL 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:
Titration of the dosage is required in patients with mild to moderate hepatic insufficiency or non-biliary cirrhosis (see section 4.4).
REGDUAL 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. Valsartan/HCT/Amlodipine Rush (GFR: > 30 mL/min). Due to the hydrochlorothiazide component, REGDUAL CO is contraindicated in patients with severe renal impairment and those with anuria (see section 4.3).

Paediatric population
The safety and efficacy of REGDUAL CO have not been established in children.

Method of administration
Oral use.
REGDUAL CO can be taken with or without food and should be administered with water.

Missed dose
If a dose is missed the advice patients who forget to take REGDUAL 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 a missed dose.

4.3 Contraindications
- hypersensitivity to valsartan, sulphonamide-derived substances (as hydrochlorothiazide) or any of the excipients listed in section 6.1.
- patients with a history of previous angioedema and current basal cell carcinomas and/or squamous cell carcinomas of the skin.
- a history of angioedema related to previous therapy with ACE inhibitors or angiotensin II receptor antagonists. Angioedema with a history of angioedema of unknown aetiology.
- 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 Sacubitril/valsartan with ACEIs/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
- concomitant use of extracorporeal administration with REGDUAL CO may lead to toxic blood concentrations of valsartan
- pregnancy and lactation (see sections 4.4 and 4.6)
- the concomitant use of REGDUAL CO with other diuretics such as aliskiren is contraindicated (see sections 4.4 and 4.5)
- severe impairment of liver function, cirrhosis and cholestasis
- refractory hypokalemia, hypokalemia, hypercalcemia and symptomatic hyperuricemia
- REGDUAL CO is contraindicated in patients with Addison's disease due to the hydrochlorothiazide component.
- REGDUAL CO is contraindicated in patients who should not be treated with REGDUAL CO as their sympathetic nervous system is not activated (see section 4.4)
- porphyria

4.4 Special warnings and precautions for use
Should a woman become pregnant while taking REGDUAL CO, the treatment should be stopped and switched to a different class of antihypertensive medicines (see section 4.3).

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 treatment with REGDUAL CO. Sodium and/or volume-depletion should be corrected before starting treatment with REGDUAL CO, for example, by reducing the diuretic dose (see section 4.2).
- symptomatic hypotension may occur after initiation of REGDUAL 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 REGDUAL CO may be continued once blood pressure has stabilised.

Serum electrolytes:
- Concomitant 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 REGDUAL CO, has been linked to hypokalemia. Potassium depletion with hypokalemia may cause cardiac and muscular effects. Hypokalemia, accompanied by neurological symptoms (nausea, progressive obtundation, apathy) has been observed in isolated cases. Regular monitoring of serum sodium concentration is recommended.
- the urinary excretion of magnesium may be increased by hydrochlorothiazide, as contained in REGDUAL CO, which may result in hypomagnesemia (see section 4.5).
- hypomagnesemia or hypokalemia, induced by hydrochlorothiazide, as contained in REGDUAL CO, may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias.
- if hypokalemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG disturbances), REGDUAL CO should be discontinued. Correction of hypokalemia and any hypomagnesemia is recommended prior to the ingestion of digitalis. Frequent monitoring is recommended.
- decreased urinary calcium excretion caused by hydrochlorothiazide, as contained in REGDUAL CO, may result in an intermittent and slightly raised serum calcium concentration. Should marked hypercalcemia occur, it may be evidence of underlying hyperparathyroidism. REGDUAL CO therapy should be discontinued before carrying out tests for parathyroid function (see section 4.5).

Other metabolic disturbances:
- In diabetic patients treated with REGDUAL CO, may increase serum levels of uric acid either causing or exacerbating hyperuricemia and precipitating gout in susceptible patients. Hydrochlorothiazide, as contained in REGDUAL CO, may also increase the frequency of gout attacks in gout patients.
- REGDUAL 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).
- REGDUAL CO should not be used in patients with biliary obstructive disorders.

Post-myocardial infarction heart failure:
- REGDUAL CO may be used in post-myocardial infarction or heart failure, commonly results in some reduction in blood pressure, but discontinuation of REGDUAL CO therapy because of continuing symptomatic hypotension is not usually necessary provided dosing procedures are followed. Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction. As a consequence of inhibition of the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin 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.
- Caution should be used when initiating treatment with concurrent administration of ACE inhibitors, beta-blockers and REGDUAL CO, as an increase in mortality has been reported on this triple therapy.

Dehydration:
- a reduction in water 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 taking hot weather because of the risk of dehydration due to excessive sweating which may result in hypotension.

Systemic lupus erythematosus:
- Hypersensitivity reactions to hydrochlorothiazide has been reported with the use of hydrochlorothiazide, as contained in REGDUAL CO.

Primary hyperaldosteronism:
- REGDUAL CO is not a hypotensive medicine for patients with primary hyperaldosteronism, 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. REGDUAL CO should be discontinued immediately in patients who develop angioedema and should not be re-administered (see sections 4.3 and 4.8).

Anaphylactic reactions:
- Cases of anaphylactic reactions have been reported with hydrochlorothiazide, as contained in REGDUAL CO, when administered to patients with allergy and bronchial asthma. If anaphylaxis occurs, it is recommended to stop the treatment. If a re-administration of REGDUAL CO is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma:
- hydrochlorothiazide, a sulphonamide, as contained in REGDUAL 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 taking the sulphonamide. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment to reverse symptoms as quickly 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 sulphonamide or penicillin allergy.

Renal artery stenosis:
- REGDUAL 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).

Hypersensitivity:
- There is experience on the safe use of REGDUAL CO in patients who have recently undergone kidney transplantation (see section 4.2).

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. Photosensitizing action of HCTZ could act as a possible mechanism for NMSC. Patients taking REGDUAL CO should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any lesions that may be suspicious of skin cancer. Advise patients to limit their exposure to sunlight and UV rays and, if exposed, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined, including histological examinations of biopsies.
- REGDUAL CO should not be used by patients who have had previous and/or current basal cell carcinoma 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 REGDUAL CO
Sorbitol:
REGDUAL CO contains lactose. Patients with the rare hereditary conditions of galactose intolerance or Lapp lactase deficiency or glucose-galactose malabsorption should not take REGDUAL CO.

Sorbitol:
The additive effect of concentrating substances and diuretics containing sorbitol or sorbitol-containing medicines should be taken into account if REGDUAL CO is taken. The content of sorbitol may be important for and may affect the bioavailability of other medicines for oral use administered concomitantly.

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 concomitant use of lithium with angiotensin converting enzyme inhibitors. Concomitant use of Sacubitril/valsartan with angiotensin receptor blockers (ARBs). Concomitant use of Furosemide and ACE inhibitors/ARBs may precipitate acute kidney injury. The administration of potassium-containing salt substitutes, other salts 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 increase potassium levels (e.g. heparin) may lead to increases in serum potassium.
REGDUAL CO and potassium-sparing diuretics should not be given together (see sections 4.3 and 4.4).

Concomitant use not recommended:
Potassium:
an orthostatic indicates that valsartan is a substrate of the benzoic uptake transporter OAT3. Co-administration of probenecid, a known inhibitor of the transporter of this drug is unknown. Co-administration of probenecid and Sacubitril/valsartan.
Co-administration of probenecid and Sacubitril/valsartan.
Co-administration of probenecid and Sacubitril/valsartan.