1.3.1.1 Professional Information for Medicines for Human Use

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

NAVIOD CO 80/12,5 (film-coated tablets)

NAVIOD CO 160/12,5 (film-coated tablets)

NAVIOD CO 160/25 (film-coated tablets)

NAVIOD CO 320/12,5 (film-coated tablets)

NAVIOD CO 320/25 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NAVIOD CO 80/12, 5 mg: Each tablet contains 80 mg valsartan and 12,5 mg hydrochlorothiazide. Contains sugar: lactose monohydrate 60 mg/tablet.

NAVIOD CO 160/12,5 mg: Each tablet contains 160 mg valsartan and 12,5 mg hydrochlorothiazide. Contains sugar: lactose monohydrate 120 mg/tablet.

NAVIOD CO 160/25 mg: Each tablet contains 160 mg valsartan and 25 mg hydrochlorothiazide. Contains sugar: lactose monohydrate 120 mg/tablet.

NAVIOD CO 320/12,5 mg: Each tablet contains 320 mg valsartan and 12, 5 mg hydrochlorothiazide. Contains sugar: lactose monohydrate 240 mg/tablet.

NAVIOD CO 320/25 mg: Each tablet contains 320 mg valsartan and 25 mg hydrochlorothiazide. Contains sugar: lactose monohydrate 240 mg/tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

NAVIOD CO 80 mg/12,5 mg:

Light orange coloured, ovaloid, beveled edge, biconvex film-coated tablets debossed with 'I' on one side and '61' on other side.

NAVIOD CO 160 mg/12,5 mg:

Dark red coloured, ovaloid, beveled edge, biconvex film-coated tablets debossed with 'I' on one side and '62' on other side.

NAVIOD CO 160 mg/25 mg:

Brown-orange coloured, ovaloid, beveled edge, biconvex film-coated tablets debossed with “I” on one side and '63' on other side.

NAVIOD CO 320 mg/12,5 mg:

Pink coloured, oval, beveled edge, biconvex film-coated tablets debossed with 'I' on one side and '64' on other side.

NAVIOD CO 320 mg/25 mg:

Yellow coloured, oval, beveled edge, biconvex film-coated tablets debossed with 'I' on one side and '65' on other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of mild to moderate hypertension.

NAVIOD 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

Posology:

The recommended dose is 1 tablet per day. When clinically appropriate either **NAVIOD CO 80/12, 5 mg**, **NAVIOD CO 160/12, 5 mg** or **NAVIOD CO 320/12, 5 mg** may be used. When necessary **NAVIOD CO 160/25 mg** or **NAVIOD CO 320/25 mg** may be used.

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

Special Populations

Use in children:

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

Use in renal impairment:

No dosage adjustment is required for patients with mild renal impairment (creatinine clearance > 70 mL/min).

Use in hepatic impairment:

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

Method of administration

Oral use.

NAVIOD CO is given orally with or without food

4.3. Contraindications

- Known hypersensitivity to valsartan, hydrochlorothiazide or to any of the excipients of **NAVIOD CO** (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 (creatinine clearance less than 30 ml/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone,

triamterene, amiloride (see section 4.4).

- 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 therapy: Concomitant administration with **NAVIOD CO** may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of **NAVIOD CO** with aliskiren-containing medicines is contraindicated (see section 4.4).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip".

4.4. Special warnings and precautions for use

Pregnancy

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

Serum electrolyte changes

Valsartan

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.

Hydrochlorothiazide

Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.

Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloraemic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium and/or volume-depleted patients

Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance.

In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur after initiation of therapy with **NAVIOD CO**. Sodium and/or volume depletion should be corrected before starting treatment with **NAVIOD CO**.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone 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.

Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. The use of **NAVIOD CO** in patients with severe chronic heart failure has not been established.

Hence, it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of **NAVIOD CO** as well may be associated with impairment of the renal function. **NAVIOD CO** should not be used in these patients.

Renal artery stenosis

NAVIOD 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 .

Primary hyperaldosteronism

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

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM) .

Renal Impairment

No dosage adjustment is required for patients with renal impairment with a creatinine clearance ≥ 30 mL/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when **NAVIOD CO** is used in patients with renal impairment.

Kidney transplantation

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

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, **NAVIOD CO** should be used with caution (see sections 4.2 and 5.2). Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

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. **NAVIOD CO** should be immediately discontinued in patients who develop angioedema, and **NAVIOD CO** should not be re-administered (see section 4.8).

Systemic lupus erythematosus

Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances

Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patient's dosage adjustments of insulin or oral hypoglycaemic medicines may be required. (2)
Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism.

Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity

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

General

Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Acute Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, 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 week of a medicine initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide 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.

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 ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore contraindicated (see sections 4.3).

NAVIOD CO should not be used concomitantly with aliskiren (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 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 / angiotensin receptor blockers whether used separately and/or concomitantly.

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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide 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 minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. **NAVIOD 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 also section 4.8).

Excipient warning

NAVIOD CO contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take **NAVIOD CO**.

4.5 Interaction with other medicines and other forms of interaction

Interactions related to both valsartan and hydrochlorothiazide

Concomitant use not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiontensin II receptor antagonist or thiazides, including hydrochlorothiazide. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with **NAVIOD CO**. If the combination proves necessary, a careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution

Other antihypertensive medicines

NAVIOD CO may increase the effects of other medicines with antihypertensive properties (e.g. guanethidine, methyldopa, vasodilators, ACEI, ARBs, beta-blockers, calcium channel blockers and DRIs).

Pressor amines (e.g. noradrenaline(norepinephrine), adrenaline(epinephrine))

Possible decreased response to pressor amines. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/day), and non-selective NSAIDs.

NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of **NAVIOD CO** and NSAIDs may lead to worsening of renal function and an increase in

serum potassium. 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 Renin-Angiotensin-Aldosterone System (RAAS) with ARBs, 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 and 4.4 .

Concomitant use not recommended

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

If a medicine that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

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 (eg. rifampin, ciclosporin) or efflux transporter (eg. ritonavir) may increase the systemic

exposure to valsartan. Exercise appropriate care when initiating or ending concomitant treatment with such medicines.

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).

No interaction

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. Digoxin and indomethacin could interact with the hydrochlorothiazide component of **NAVIOD CO** (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide

Concomitant use requiring caution

Medicines affecting serum potassium level

The hypokalaemic effect of hydrochlorothiazide may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic

hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives.

If these medicines are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised (see section 4.4).

Medicines that could induce torsades de pointes

Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicines that could induce torsades de pointes, in particular Class Ia and Class III antidysrhythmics and some antipsychotics.

Medicines affecting serum sodium level

The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicines such as antidepressants, antipsychotics, antiepileptics, etc. Caution is advised in long-term administration of these medicines.

Digitalis glycosides

Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects favouring the onset of digitalis-induced cardiac dysrhythmias (see section 4.4).

Calcium salts and vitamin D

Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics with calcium salts may cause hypercalcaemia in patients pre-disposed for

hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

Antidiabetic medicines (oral age medicines and insulin)

Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary.

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

Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

Medicines used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)

Dose adjustment of uricosuric medicines may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic medicines and other medicines affecting gastric motility

The bioavailability of thiazide-type diuretics may be increased by anticholinergic medicines (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal

motility and the stomach emptying rate. Conversely, it is anticipated that prokinetic medicines such as cisapride may decrease the bioavailability of thiazide-type diuretics.

Amantadine

Thiazides, including hydrochlorothiazide, may increase the risk of adverse effects caused by amantadine.

Ion exchange resins

Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide 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.

Cytotoxic medicines

Thiazides, including hydrochlorothiazide, may reduce renal excretion of cytotoxic medicines (e.g. cyclophosamide, methotrexate) and potentiate their myelosuppressive effects.

Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)

Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Ciclosporin

Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Alcohol, barbiturates or narcotics

Concomitant administration of thiazide diuretics with medicines that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation activity) may potentiate orthostatic hypotension.

Methyldopa

There have been isolated reports of haemolytic anaemia in patients receiving concomitant treatment with methyldopa and hydrochlorothiazide.

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing age

Women of childbearing age should ensure effective contraception**.**

Pregnancy

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

Breast-feeding

No information is available regarding the use of valsartan during breast-feeding. Hydrochlorothiazide is excreted in human milk. Therefore, the use of NAVIOD CO during breast-feeding is contraindicated (see section 4.3). Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new born or preterm infant.

Fertility

No fertility data is available

4.7 Effects on ability to drive and use machines

No studies on the effect of **NAVIOD CO**, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Table 1. Frequency of adverse reactions with valsartan/hydrochlorothiazide:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Metabolism and nutrition disorders	Less frequent	Dehydration
Nervous system disorders	Less frequent	Dizziness, paraesthesia
	Frequency unknown	Syncope
Eye disorders	Less frequent	Vision blurred
Ear and labyrinth disorders	Less frequent	Tinnitus
Vascular disorders	Less frequent	Hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Cough
	Frequency unknown	Non cardiogenic pulmonary oedema
Gastrointestinal disorders	Less frequent	Diarrhoea
Musculoskeletal and connective tissue disorders	Less frequent	Myalgia, arthralgia
Renal and urinary disorders	Frequency unknown	Impaired renal function

General disorders and administration site conditions	Less frequent	Fatigue
Investigations	Frequency unknown	Serum uric acid increased, serum bilirubin and serum creatinine increased, hypokalaemia, hyponatraemia, elevation of blood urea nitrogen, neutropenia

Additional information on the individual components

Adverse reactions previously reported with one of the individual components may be potential undesirable effects with **NAVIOD CO** as well, even if not observed in clinical trials or during post-marketing period.

Table 2. Frequency of adverse reactions with valsartan

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and the lymphatic system disorders	Frequency unknown	Decrease in haemoglobin, decrease in haematocrit, thrombocytopenia
Immune system disorders	Frequency unknown	Other hypersensitivity/allergic reactions including serum sickness

Metabolism and nutrition disorders	Frequency unknown	Increase of serum potassium, hyponatraemia
Psychiatric disorders	Frequency unknown	Decreased libido
Ear and labyrinth disorders	Less frequent	Vertigo
Vascular disorders	Frequency unknown	Vasculitis
Gastrointestinal disorders:	Less frequent	Abdominal pain
Hepatobiliary disorders	Frequency unknown	Elevation of liver function values
Skin and subcutaneous tissue disorders:	Frequency unknown	Angioedema, dermatitis bullous, rash, pruritus
Renal and urinary disorders:	Frequency unknown	Renal failure

Table 3. Frequency of adverse reactions with hydrochorothiazide

MedDRA system organ class	**Frequency**	**Adverse reactions**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia sometimes with purpura, agranulocytosis, leucopenia, haemolytic anaemia, bone marrow failure
	Frequency unknown	Aplastic anaemia
Immune system disorders	Less frequent	Hypersensitivity reactions
Metabolism and nutrition disorders	Frequent	Hypokalaemia, increased blood lipids (mainly at higher doses), hyponatraemia, hypomagnesaemia, hyperuricaemia,
	Less frequent	Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state, hypochloraemic alkalosis

Psychiatric disorders	Less frequent	Depression, sleep disturbances
Nervous system disorders	Less frequent	Headache, dizziness, paraesthesia
Eye disorders	Less frequent	Visual impairment
	Frequency unknown	Acute angle-closure glaucoma
Cardiac disorders	Less frequent	Cardiac dysrhythmias
Vascular disorders	Frequent	Postural hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory distress including pneumonitis and pulmonary oedema
Gastrointestinal disorders	Frequent	Loss of appetite, mild nausea and vomiting
	Less frequent	Constipation, gastrointestinal discomfort, diarrhoea, pancreatitis
Hepatobiliary disorders	Less frequent	Intrahepatic cholestasis or jaundice
Renal and urinary disorders	Frequency unknown	Renal dysfunction, acute renal failure

Skin and subcutaneous tissue disorders	Frequent	Urticaria and other forms of rash
	Less frequent	Photosensitisation, necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
	Frequency unknown	Erythema multiforme
Musculoskeletal and connective tissue disorders	Frequency unknown	Muscle spasm
Reproductive system and breast disorders	Frequent	Impotence
General disorders and administration site conditions	Frequency unknown	Pyrexia, asthenia

c. 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac dysrhythmias and muscle spasms.

Treatment

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.
If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly.
Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis .

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, valsartan and diuretics; ATC code: C09D A03

Pharmacological classification: A.7.1.3 Vascular medicines – other hypotensives.

Valsartan is an orally active, specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the Angiotensin 1 receptor subtype, which is responsible for the known actions of angiotensin II. Valsartan does not exhibit any partial agonist activity at the Angiotensin 1 receptor and has much (about 20 000 fold) greater affinity for the Angiotensin 1 receptor than for the Angiotensin 2 receptor.
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 action is achieved within 4 to 6 hours. The effect persists 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 therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.
The site of action of the diuretic effect of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high affinity receptor in the renal cortex with the primary binding site for the thiazide diuretic action and inhibition of NaCl

transport in the distal convoluted tubule. The mechanisms of the antihypertensive effects of the thiazide diuretics are not fully known.

5.2 Pharmacokinetic properties

Valsartan/hydrochlorothiazide

The systemic availability of hydrochlorothiazide is reduced by about 30 % when co-administered with valsartan. The kinetics of valsartan are not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide, since controlled clinical trials have shown a clear anti-hypertensive effect, greater than that obtained with either active substance given alone, or placebo.

Valsartan

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2 – 4 hours. Mean absolute bioavailability is 23 %. 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 h 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.

Distribution

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94 – 97 %), mainly serum albumin.

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 (t½α <1 h and t½ß about 9 h). Valsartan is primarily eliminated in faeces (about 83 % of dose) and urine (about 13 % of dose), mainly as unchanged medicine. Following intravenous administration, plasma clearance of valsartan is about 2L /h and its renal clearance is 0,62L /h (about 30 % of total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide

Absorption

The absorption of hydrochlorothiazide, after an oral dose, is rapid (t_{max} about 2 h). The increase in mean AUC is linear and dose proportional in the therapeutic range.
The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 60 to 80 % after oral administration.

Distribution

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.

Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. There is more than 95 % of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Special populations

Elderly

A significantly higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Renal impairment

At the recommended dose of **NAVIOD CO** no dose adjustment is required for patients with mild renal impairment.

In patients with moderate to severe renal impairment (creatinine clearance < 70 mL/min) and patients undergoing dialysis no data are available for **NAVIOD CO**. Valsartan is highly bound to plasma protein and is not to be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed. Hydrochlorothiazide is contraindicated in patients with severe renal impairment (see section 4.3).

Hepatic impairment

In a pharmacokinetics trial in patients with mild to moderate hepatic dysfunction, exposure to valsartan was increased approximately 2-fold compared with healthy volunteers (see sections 4.2 and 4.4).

There is no data available on the use of valsartan in patients with severe hepatic dysfunction . Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, Microcrystalline Ph.Eur (Avicel PH 101)

Cellulose, Microcrystalline Ph.Eur (Avicel PH 112)

Lactose Monohydrate (Pharmatose 200M) Ph.Eur.

Crospovidone (Polyplasdone XL 10) Ph.Eur.

Silica, Colloidal Anhydrous (Aerosil-200) Ph.Eur.

Hypromellose (Methocel E5LV premium) Ph.Eur.

Sodium Lauryl Sulphate (Texapon K 12 P PH) Ph.Eur.

Talc Ph.Eur.

Magnesium Stearate Ph.Eur

Ingredients of Coating material:

NAVIOD CO 80 /12,5 mg:

Opadry 03F84793 Pink Powder IH

NAVIOD CO 160 /12,5 mg:

Opadry 03F86845 Brown Powder IH

NAVIOD CO 160 /25 mg:

Opadry 03F86762 Brown Powder IH

NAVIOD CO 320 /12,5 mg:

Opadry 03F84782 Pink Powder IH

NAVIOD CO 320 /25 mg:

Opadry 03F82604 Yellow Powder IH

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

The tablets should be stored in marketed, moisture-proof containers.

Store at or below 25°C.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

NAVIOD CO 80 /12,5mg; 160/12,5 mg; 160/25 mg; 320/12,5 mg; 320/25 mg:

Blister Pack

250 Micron PVC laminated with 51 Micron Aclar - Aluminium foil blister pack:

Blister pack comprises of 250 Micron PVC laminated with 51 Micron Aclar as the forming material and 25 µ Aluminum foil with 7 g/m2 heat seal lacquer as the lidding material.

Valsartan/Hydrochlorothiazide Tablets packed in above blisters shall be further packed in preprinted cartons with package leaflet according to the approved pack size.

Pack size: Printed cardboard carton containing 3 blisters of 10 film coated tablets each.

HDPE Container Pack:

For 80/12,5 mg:

White opaque round 40 ml HDPE container with 33 mm neck finish closed with 33 mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner.

Each HDPE container shall contain 1 no of 1 g silica gel sachet.

These HDPE bottles shall be packed in pre-printed carton with a packaging leaflet.

Pack Size: 30's (HDPE)

For 160/12,5 mg and 160/25 mg:

White opaque round 60 ml HDPE container with 33 mm neck finish closed with 33 mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner.

Each HDPE container shall contain 1 no of 1 g silica gel sachet.

These HDPE bottles shall be packed in pre-printed carton with a packaging leaflet.

Pack Size: 30's (HDPE)

For 320/12,5 mg and 320/25 mg:

White opaque round 100 ml HDPE container with 38 mm neck finish closed with 38 mm white opaque polypropylene stock ribbed closure with wad having induction sealing liner.

Each HDPE container shall contain 1 no of 1 g silica gel sachet.

These HDPE bottles shall be packed in pre-printed carton with a packaging leaflet.

Pack Size: 30's (HDPE)

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8 REGISTRATION NUMBERS

NAVIOD CO 80/12,5 mg: 48/7.1.3/0861

NAVIOD CO 160/12,5 mg: 48/7.1.3/0862

NAVIOD CO 160/25 mg: 48/7.1.3/0863

NAVIOD CO 320/12,5 mg: 48/7.1.3/0864

NAVIOD CO 320/25 mg: 48/7.1.3/0865

9 DATE OF FIRST AUTHORISATION

18 May 2022

10 DATE OF REVISION OF TEXT

6 March 2023