PROFESSIONAL INFORMATION (CLEAN)

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

DIPTATRIS 5 mg/160 mg/12,5 mg Film-coated tablets

DIPTATRIS 5 mg/160 mg/25 mg Film-coated tablets

DIPTATRIS 10 mg/160 mg/12,5 mg Film-coated tablets

DIPTATRIS 10 mg/160 mg/25 mg Film-coated tablets

DIPTATRIS 10 mg/320 mg/25 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DIPTATRIS 5 mg/160 mg/12,5 mg: Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg of amlodipine base), 160 mg of valsartan and 12,5 mg hydrochlorothiazide.

DIPTATRIS 5 mg/160 mg/ 25 mg: Each film-coated tablet contains 6,94 mg amlodipine besylate (equivalent to 5 mg of amlodipine base), 160 mg of valsartan and 25 mg hydrochlorothiazide.

DIPTATRIS 10 mg/160 mg/12,5 mg: Each film-coated tablet contains 13,88 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 160 mg of valsartan and 12,5 mg hydrochlorothiazide.

DIPTATRIS 10 mg/160mg/25 mg: Each film-coated tablet contains 13,88 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 160 mg of valsartan and 25 mg hydrochlorothiazide.

DIPTATRIS 10 mg/320 mg/25 mg: Each film-coated tablet contains 13,88 mg amlodipine besylate (equivalent to 10 mg of amlodipine base), 320 mg of valsartan and 25 mg hydrochlorothiazide.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

DIPTATRIS 5 mg/160 mg/ 12,5 mg:

A white to off-white, film-coated, oval, biconvex, bevelled edge tablet debossed with "AVH1" on one side of the tablet and "M" on the other side.

DIPTATRIS 5 mg/160 mg/ 25 mg:

A yellow, film-coated, oval, biconvex, bevelled edge tablet debossed with "AVH3" on one side of the tablet and "M" on the other side.

DIPTATRIS 10 mg/160 mg/ 12,5 mg:

An orange, film-coated, oval, biconvex, bevelled edge tablet debossed with "AVH2" on one side of the tablet and "M" on the other side.

DIPTATRIS 10 mg/160 mg/ 25 mg:

Alight brown-yellow, film-coated, oval, biconvex, bevelled edge tablet debossed with AVH4" on one side of the tablet and "M" on the other side.

DIPTATRIS 10 mg/320 mg/ 25 mg:

Alight brown-yellow, film-coated, oval, biconvex, bevelled edge tablet debossed with "AVH5" on one side of the tablet and "M" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in patients stabilised on individual components given at the same doses.

DIPTATRIS is not indicated for the initial therapy of hypertension (see section 4.2).

4.2 Posology and method of administration

Posology:

The recommended dose is one tablet per day (the 5 strengths are listed under section 2).

If a tablet shows signs of cracking the tablet should not be taken.

Patients stabilised with valsartan, amlodipine and hydrochlorothiazide (HCTZ) from separate tablets may be switched to DIPTATRIS containing the same component doses.

The maximum antihypertensive effect of DIPTATRIS is reached within two weeks after a change in dose. The maximum recommended dose of DIPTATRIS is 10/320/25 mg.

In elderly:

No adjustment of the initial dose is required for elderly patients (see section 5.2).

Children and adolescents (below 18 years):

DIPTATRIS is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Renal and hepatic impairment:

No dosage adjustment is required for patients with mild to moderate renal impairment, but caution should be exercised when administering DIPTATRIS to patients with hepatic impairment or biliary obstructive disorders (see section 4.4 and 4.8). Due to the hydrochlorothiazide component, DIPTATRIS is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients with severe hepatic impairment (see section 4.3 and 5.2).

Method of administration

Oral use.

DIPTATRIS can be taken with or without food. It is recommended to take DIPTATRIS with some water.

4.3 Contraindications

- Known hypersensitivity to amlodipine, valsartan, hydrochlorothiazide and other sulfonamides, or to any of the excipients of DIPTATRIS (see section 6.1).
- The use of DIPTATRIS during pregnancy and lactation is contraindicated

- (see section 4.6). DIPTATRIS should be discontinued as soon as possible when pregnancy is suspected.
- A history of angioedema related to previous therapy with angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Severe hepatic impairment (Child-Pugh C).
- DIPTATRIS should not be given to patients with Addison's disease.
- Anuria, severe renal impairment (creatinine clearance less than 30 ml/min).
- Lithium therapy: Concomitant administration with DIPTATRIS may lead to toxic blood concentrations of lithium (see section 4.5).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.
- Safety and efficacy have not been established in children, less than 18 years old.
- Safety has not been established in porphyria.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis and mitral valve stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- The concomitant use of DIPTATRIS with aliskiren-containing products is contraindicated.
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin blockers is

contraindicated in patients with moderate (Creatinine Clearance <60 ml/min) to severe renal impairment (creatinine clearance <30 ml/min) and in elderly patients.

- 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 DIPTATRIS, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and 4.6)

When pregnancy is detected, DIPTATRIS should be discontinued as soon as possible and switched to a different class of antihypertensive medicine (see section 4.3 and 4.6).

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Children

Safety and efficacy of DIPTATRIS in patients aged below 18 years has not been established.

Sodium- and/or volume depleted patients

Excessive hypotension, including orthostatic hypotension was seen in 1,7 % of patients treated with the maximum dose of DIPTATRIS (10/320/25 mg) compared to 1,8 % of valsartan/HCTZ (320/25 mg) patients, 0,4 % of amlodipine/valsartan (10/320 mg) patients, and 0,2 % of HCTZ/amlodipine (25/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension. In patients with an activated renin-angiotensin system, such as volume-and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. This condition should be corrected prior to administration of DIPTATRIS, or the treatment should start under close medical supervision. If excessive hypotension occurs with DIPTATRIS, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of 0,9 % sodium chloride solution. Treatment can be continued once blood pressure has been stabilised.

Renal impairment

No dosage adjustment of DIPTATRIS is required for patients with mild to moderate renal impairment. Due to the hydrochlorothiazide component, DIPTATRIS is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 ml/min), (see section 4.3).

Renal artery stenosis

DIPTATRIS should not be used in bilateral renal artery stenosis and renal artery stenosis in patients with a single kidney, since blood urea and serum creatinine may increase in these patients (see section 4.3).

Kidney transplantation

There is no experience with the use of DIPTATRIS in patients with recent kidney transplantation.

Hepatic impairment

Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolised by the liver. Particular caution should be exercised when administering DIPTATRIS to patients with hepatic impairment or biliary obstructive disorders. Because of hydrochlorothiazide, DIPTATRIS is not recommended in patients with severe hepatic impairment (see section 4.3).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy (see section 4.3).

Serum electrolyte changes:

Hydrochlorothiazide

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium

levels (heparin, etc.) could lead to hyperkalaemia and should be used with caution. Hypokalaemia has been reported under treatment with thiazide diuretics including hydrochlorothiazide. Frequent monitoring of potassium is recommended (see section 4.3).

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

Amlodipine -Valsartan - Hydrochlorothiazide

In a controlled trial the opposite effects of valsartan 320 mg and hydrochlorothiazide 25 mg on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals, especially in patients with other risk factors such as impaired renal function, treatment with other medicines or history of prior electrolyte imbalances.

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 patients dosage adjustments of insulin or oral hypoglycaemic medicines may be required.

Due to the hydrochlorothiazide component, DIPTATRIS is contraindicated in symptomatic hyperuricaemia. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. DIPTATRIS is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. DIPTATRIS should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE inhibitors, ARBs 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, ARBs and aliskiren is therefore contraindicated (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

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 minimise the risk of skin cancer.

Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. Hydrochlorothiazide should not be used in patients who have experienced previous NMSC (see section 4.3).

Concomitant use with fluoroquinolones

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.

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 medicinal products including ACE inhibitors. DIPTATRIS should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Heart failure and coronary artery disease/post-myocardial infarction

As a consequence of the inhibition of the renin-angiotensin-aldosterone system, 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 renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or

progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of DIPTATRIS 10 mg/320 mg/25 mg since available data in these patient populations is limited.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is not activated. Therefore, DIPTATRIS is not recommended in this population.

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

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with DIPTATRIS, 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.

Choroidal effusion, acute myopia and secondary acute angle-closure glaucoma

Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in choroidal effusion with visual field defect, 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 treatment 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 sulphonamide or penicillin allergy.

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.

Elderly (age 65 years or over)

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of DIPTATRIS 10 mg/320 mg/25 mg, since available data in this patient population are limited.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use not recommended:

Individual component	**Known interaction with the following components**	**Effect of the interaction with other medicines**
Valsartan and HCT	Lithium	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists including valsartan or thiazides.

		Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with DIPTATRIS. Therefore, careful monitoring of serum lithium concentrations is recommended during concomitant use.
Valsartan	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, frequent monitoring of potassium plasma levels is advised.
Amlodipine	Grapefruit or grapefruit juice	Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in

		increased blood pressure lowering effects.

Caution required with concomitant use:

Individual component	**Known interaction with the following components**	**Effect of the interaction with other medicines**
Amlodipine	CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir)	Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
Amlodipine	CYP3A4 inducers	Upon co-administration of known inducers of the CYP3A4, the

	(anticonvulsant medicines [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum [St. John's wort])	plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medicine particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).
	Simvastatin	Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.
	Dantrolene (infusion)	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia

		after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the concomitant administration of calcium channel blockers such as amlodipine with intravenous dantrolene be avoided in patients susceptible to malignant hyperthermia, and in the management of malignant hyperthermia.
Valsartan and HCT	Non-steroidal anti-inflammatory Drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid (>3 g/day), and nonselective NSAIDs	NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of DIPTATRIS 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.
Valsartan	Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)	The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
Hydrochlorothiazide	Alcohol, barbiturates or narcotics	Concomitant administration of thiazide diuretics with substances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system

		activity or direct vasodilatation) may potentiate orthostatic hypotension.
	Amantadine	Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.
	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 substances such as cisapride may decrease the bioavailability of thiazide-type diuretics.
	Antidiabetic medicines (e.g. insulin and oral antidiabetic medicines)	Thiazides may alter glucose tolerance. It may prove necessary to readjust the dosage

	- Metformin	of insulin and of oral antidiabetic medicines. 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.
	Ciclosporin	Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.
	Cytotoxic medicines	Thiazides, including hydrochlorothiazide,

		may reduce the renal excretion of cytotoxic medicines (e.g., cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
	Digitalis glycosides	Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects, favouring the onset of digoxin-induced cardiac dysrhythmias.
	Iodine contrasting products	In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be re-hydrated before the administration.
	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.
	Medicines affecting serum potassium levels:	The hypokalaemic effect of diuretics may be increased by kaliuretic diuretics, corticosteroids, ACTH, laxatives, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives. If these medicines are to be prescribed with the amlodipine /valsartan /hydrochlorothiazide combination, monitoring of potassium plasma levels is advised.

	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 indicated in long-term administration of these medicines.
	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 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 dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.
	Methyldopa	There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
	Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)	Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives
	Other anti-hypertensive medicines	Thiazides potentiate the antihypertensive action of other antihypertensive medicines (e.g. guanethidine, methyldopa,

		beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs and Direct Renin Inhibitors [DRIs]).
	Pressor amines (e.g. noradrenaline, adrenaline)	Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.
	Vitamin D and calcium salts	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 may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D-mediated

		conditions) by increasing tubular calcium reabsorption.

Individual component	**Known interaction with the following components**
Amlodipine	In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, aluminium hydroxide gel, magnesium hydroxide and simeticone, cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic medicines.
Valsartan	In monotherapy with valsartan, no medicine interactions of clinical significance have been found with the following medicines: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels. 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).

Dual blockade of the RAAS with ARBs, ACE inhibitors, 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)

4.6 Fertility, pregnancy and lactation

Pregnancy

DIPTATRIS is contraindicated in pregnancy as teratogenicity has been shown in experimental animals. Medicines affecting the renin-angiotensin system, such as DIPTATRIS, can cause foetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, DIPTATRIS should be discontinued as soon as possible. Women of childbearing age should use effective contraception.

Breast-feeding

It is not known whether valsartan and/or amlodipine are excreted inhuman milk. Valsartan was excreted in the milk of lactating rats. Hydrochlorothiazide is excreted into breast milk. DIPTATRIS is contraindicated in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or using machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

a) Summary of adverse effects

The safety profile of DIPTATRIS presented below is based on clinical studies performed with amlodipine/valsartan/HCT and the known safety profile of the individual components amlodipine, valsartan and hydrochlorothiazide.

Adverse reactions were generally mild and transient in nature and only infrequently required discontinuation of therapy. The most common reasons for discontinuation of therapy with amlodipine/valsartan/HCT were dizziness and hypotension.

b) Tabulated summary of adverse reactions

The following adverse reactions, listed by MedDRA System Organ Class and frequency, concern (amlodipine/valsartan/HCT) and amlodipine, valsartan and HCT individually.

System organ class	Adverse reactions	Frequency			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
Infections and infestations	Viral infections, upper respiratory tract infection, sinusitis, pharyngitis, rhinitis			Frequency unknown	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma	--	--	--	Frequency unknown
Blood and lymphatic system disorders	Agranulocytosis, bone marrow failure	--	--	--	Less frequent
	Haemoglobin and haematocrit decreased	---	--	Frequency unknown	--
	Haemolytic anaemia	--	--	--	Less frequent
	Leukopenia	—	Less frequent	—	Less frequent
	Neutropenia	---	--	Frequency unknown	--
	Thrombocytopenia,	---	Less	Frequency	Less

System organ class	**Adverse reactions**	**Frequency**			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
	sometimes with purpura		frequent	unknown	frequent
	Aplastic anaemia	---	---	---	Frequency unknown
Immune system disorders	Hypersensitivity	---	Less frequent	Frequency unknown	Less frequent
Metabolism and nutrition disorders	Anorexia	Less frequent	---	---	---
	Hypercalcaemia	Less frequent	---	---	Less frequent
	Hyperglycaemia	---	Less frequent	---	Less frequent
	Hyperlipidaemia	Less frequent	---	---	Frequent
	Hyperuricaemia	Less frequent	---	---	Frequent
	Hypochloraemic alkalosis	---	---	---	Less frequent
	Hypokalaemia	Frequent	---	---	Frequent
	Hypomagnesaemia	---	---	---	Frequent
	Hyponatraemia	Less frequent	---	---	Frequent
	Worsening of	---	---	---	Less

System organ class	Adverse reactions	Frequency			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
	diabetic metabolic state				frequent
Psychiatric disorders	Depression	---	Less frequent	---	Less frequent
	Insomnia/sleep disorders	Less frequent	Less frequent	---	Less frequent
	Mood swings	---	Less frequent	---	---
	Confusion	---	Less frequent	---	---
	Decreased libido	-	-	Frequency unknown	-
Nervous system disorders	Coordination abnormal	Less frequent	---	---	---
	Dizziness	Frequent	Frequent	---	Less frequent
	Dizziness postural, dizziness exertional	Less frequent	---	---	---
	Dysgeusia	Less frequent	Less frequent	---	---
	Extrapyramidal syndrome	---	Frequency unknown	---	---
	Headache	Frequent	Frequent	---	Less frequent
	Hypertonia	---	Less	---	---

System organ class	Adverse reactions	Frequency			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
			frequent		
	Lethargy	Less frequent	---	---	---
	Paraesthesia	Less frequent	Less frequent	---	Less frequent
	Peripheral neuropathy, neuropathy	Less frequent	Less frequent	---	---
	Somnolence	Less frequent	Frequent	---	---
	Syncope	Less frequent	Less frequent	---	---
	Tremor	---	Less frequent	---	---
	Hypoesthesia	---	Less frequent	---	---
Eye disorders	Acute angle-closure glaucoma	---	---	---	Frequency unknown
	Visual disturbance	---	Less frequent	---	---
	Visual impairment	Less frequent	Less frequent	---	Less frequent
	Diplopia	Less frequent	Less frequent		Less frequent
	Choroidal effusion	---	---	---	Frequency

System organ class	**Adverse reactions**	**Frequency**			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
					unknowm
Ear and labyrinth disorders	Tinnitus	---	Less frequent	---	---
	Vertigo	Less frequent	---	Less frequent	---
Cardiac disorders	Palpitations	---	Frequent	---	---
	Tachycardia	Less frequent	---	---	---
	Dysrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	---	Less frequent	---	Less frequent
	Myocardial infarction	---	Less frequent	---	---
Vascular disorders	Flushing	--	Frequent	--	--
	Hypotension	Frequent	Less frequent	--	--
	Orthostatic hypotension	Less frequent	--	--	Frequent
	Phlebitis, thrombophlebitis	Less frequent	--	--	--

System organ class	Adverse reactions	Frequency			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
	Vasculitis	--	Less frequent	Frequency unknown	--
Respiratory, thoracic and mediastinal disorders	Cough	Less frequent	Less frequent	Less frequent	--
	Dyspnoea	Less frequent	Less frequent	--	--
	Respiratory distress, pulmonary oedema, pneumonitis	--	--	--	Less frequent
	Rhinitis	--	Less frequent	--	--
	Throat irritation	Less frequent	--	--	--
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Less frequent	Frequent	Less frequent	Less frequent
	Breath odour	Less frequent	--	--	--
	Change of bowel habit	--	Less frequent	--	--
	Constipation	--	--	--	Less frequent

System organ class	Adverse reactions	Frequency			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
	Decreased appetite	--	--	--	Frequent
	Diarrhoea	Less frequent	Less frequent	--	Less frequent
	Dry mouth	Less frequent	Less frequent	--	--
	Dyspepsia	Frequent	Less frequent	--	--
	Gastritis	--	Less frequent	--	--
	Gingival hyperplasia	--	Less frequent	--	--
	Nausea	Less frequent	Frequent	--	Frequent
	Pancreatitis	--	Less frequent	--	Less frequent
	Vomiting	Less frequent	Less frequent	--	Frequent
Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Less frequent	Frequency unknowm	--
	Hepatitis	--	Less frequent	--	--

System organ class	Adverse reactions	Frequency			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
	Intrahepatic cholestasis, jaundice	--	Less frequent	--	Less frequent
Skin and subcutaneous tissue disorders	Alopecia	--	Less frequent	--	--
	Angioedema	--	Less frequent	Frequency unknown	--
	Dermatitis bullous	--	--	Frequency unknown	--
	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus	--	--	--	Less frequent
	Erythema multiforme	--	Less frequent	--	Frequency unknown
	Exanthema	--	Less frequent	--	--
	Hyperhidrosis	Less frequent	Less frequent	--	--
	Photosensitivity reaction	--	Less frequent	--	Less frequent
	Pruritus	Less frequent	Less frequent	Frequency unknown	--
	Purpura	--	Less	--	Less

System organ class	Adverse reactions	Frequency			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
			frequent		frequent
	Rash	--	Less frequent	Frequency unknown	Frequent
	Skin discoloration	--	Less frequent	--	--
	Urticaria and other forms of rash	--	Less frequent	--	Frequent
	Vasculitis necrotising and toxic epidermal necrolysis	--	Frequency unknown	--	Less frequent
	Exfoliative dermatitis	--	Less frequent	--	--
	Stevens-Johnson syndrome	--	Less frequent	--	--
	Quincke oedema	--	Less frequent	--	--
Musculoskeletal and connective tissue disorders	Arthralgia	--	Less frequent	--	--
	Back pain	Less frequent	Less frequent	--	--
	Joint swelling	Less frequent	--	--	--
	Muscle spasm	Less frequent	Less frequent	--	Frequency unknown

System organ class	**Adverse reactions**	**Frequency**			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
	Muscular weakness	Less frequent	--	--	--
	Myalgia	Less frequent	Less frequent	Frequency unknown	--
	Pain in extremity	Less frequent	--	--	--
	Ankle swelling	--	Frequent	--	--
Renal and urinary disorders	Blood creatinine increased	Less frequent	--	Frequency unknown	--
	Micturition disorder	--	Less frequent	--	--
	Nocturia	--	Less frequent	--	--
	Pollakiuria	Frequent	Less frequent	--	--
	Renal dysfunction	--	--	--	Frequency unknown
	Acute renal failure	Less frequent	--	--	Frequency unknown
	Renal failure and impairment	--	--	Frequency unknown	Less frequent
Reproductive system and	Impotence	Less frequent	Less frequent	--	Frequent

System organ class	**Adverse reactions**	**Frequency**			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
breast disorders	Gynaecomastia	--	Less frequent	--	--
General disorders and administration site conditions	Abasia, gait disturbance	Less frequent	--	--	--
	Asthenia	Less frequent	Less frequent	--	Frequency unknown
	Discomfort, malaise	Less frequent	Less frequent	--	--
	Fatigue	Frequent	Frequent	Less frequent	--
	Non cardiac chest pain	Less frequent	Less frequent	--	--
	Oedema	Frequent	Frequent	--	--
	Pain	--	Less frequent	--	--
	Pyrexia	--	--	--	Frequency unknown
Investigations	Lipids increased	--	--	--	Frequent
	Blood urea nitrogen increased	Less frequent	--	Frequency unknown	--
	Blood uric acid increased	Less frequent	--	--	--
	Glycosuria	--	--	--	Less frequent
	Blood potassium	Less	--	--	--

System organ class	Adverse reactions	Frequency			
		Amlodipine/valsartan / HCT	**Amlodipine**	**Valsartan**	**HCT**
	decreased	frequent			
	Blood potassium increased	--	--	Frequency unknown	--
	Weight increase	Less frequent	Less frequent	--	--
	Weight decrease	--	Less frequent	--	--

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 section 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 & Quality Problem Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/

4.9 Overdose

There is no experience of overdose with DIPTATRIS. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness.

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to DIPTATRIS overdose calls for active cardiovascular support including frequent monitoring of cardiac andrespiratory function, elevation of extremities and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis whereas clearance of HCTZ will be achieved by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Vascular medicines - other hypotensives

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists, other combinations, ATC code: C09DX01

DIPTATRIS combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class, valsartan to the angiotensin II (Ang II) antagonist class and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine

The amlodipine component of DIPTATRIS inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing a reduction in peripheral vascular resistance and reduction in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilatation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a

significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients. In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

Haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Valsartan:

Valsartan is an orally active, and specific angiotensin II receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20 000 fold) greater affinity for the AT1 receptor than for the AT2 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 reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after administration . During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Hydrochlorothiazide

The site of action 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 as the primary binding site for the thiazide diuretic action and inhibition of sodium chloride transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter perhaps by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms: - directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

5.2 Pharmacokinetic properties

Linearity:

Amlodipine, valsartan and HCTZ exhibit linear pharmacokinetics.

Amlodipine

Absorption: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been calculated as between 64 % and 80 %. Amlodipine bioavailability is unaffected by food ingestion.

Distribution: Volume of distribution is approximately 21 L/kg. In vitro studies with amlodipine have shown that approximately 97,5 % of circulating compound is bound to plasma proteins.

Biotransformation: Amlodipine is extensively {approximately 90 %) metabolised in the liver to inactive metabolites with 10 % of the parent compound and 60 % of the metabolites excreted in the urine.

Excretion: Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7-8 days. Ten per cent of original amlodipine and 60 % of amlodipine metabolites are excreted in urine.

Valsartan:

Absorption: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability is 23 %. Valsartan shows multiexponential decay kinetics (t½α <1 h and t½ß about 9 h). Food decreases the 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 group. This reduction in AUC, however, is not accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution: 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 transformed 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.

Excretion: Valsartan is primarily eliminated in faeces (about 83 % of dose) and urine (about 13 % of dose) mainly as unchanged compound. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0,62 L/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. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical

importance. Absolute bioavailability of hydrochlorothiazide is 60-80 % after oral administration.

Distribution: The distribution and elimination kinetics have generally been described as a bi-exponential decay function, with a terminal half-life of 6-15 h. 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.

Biotransformation: HCTZ is eliminated as unchanged compound.

Excretion: There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. More than 95 % of the absorbed dose being excreted as unchanged compound in the urine.

Amlodipine/ Valsartan/Hydrochlorothiazide:

Following oral administration of DIPTATRIS in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and HCTZ are reached in 6-8 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and HCTZ from DIPTATRIS are the same as when administered as individual dosage forms.

Special populations

Paediatrics:

No pharmacokinetic data are available in the paediatric population for DIPTATRIS.

Elderly Patients:

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life.

Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but 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.

Since the three components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended (see section 4.2).

Renal impairment:

The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Patients with mild to moderate renal impairment may therefore receive the usual initial dose (see sections 4.2 and 4.4).

Hepatic impairment:

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60 % in AUC. On average, in patients

with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Care should be exercised in patients with liver disease (see sections 4.2 and 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Colloidal silicon dioxide

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate

Film Coat:

HPMC 2910/ Hypromellose (E464)

Iron Oxide Red (E172)

Iron Oxide Yellow (E172)

Macrogol/ PEG 6000 (E1521)

Talc (E553b)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

HDPE bottle pack (marketable pack) comprises of round, blue, opaque, high-density polyethylene (HDPE) bottle with blue opaque polypropylene child resistant closure with wad containing aluminium induction sealing liner. The HDPE bottle pack may be placed in an outer cardboard carton along with desiccant based on commercial requirement. Pack size: 30’s.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 HOLDER OF CERTIFICATE OF REGISTRATION

VIATRIS HEALTHCARE (PTY) LTD

4 Brewery Street

Isando

Gauteng

Republic of South Africa

8 REGISTRATION NUMBERS

Diptatris 5 mg/160 mg/ 12.5 mg: TBA

Diptatris 5 mg/160 mg/ 25 mg: TBA

Diptatris 10 mg/160 mg/ 25 mg: TBA

Diptatris 10 mg/320 mg/ 25 mg: TBA

Diptatris 10 mg/160 mg/ 12.5 mg: TBA

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the registration certificate

10 DATE OF REVISION OF THE TEXT