Viacoram

SCHEDULING STATUS **S3**

1. NAME OF THE MEDICINE

Viacoram 3,5/2,5 mg tablets

Viacoram 7/5 mg tablets

Viacoram 14/10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Viacoram 3,5/2,5 mg tablets.

One tablet contains 2,378 mg perindopril equivalent to 3,5 mg perindopril arginine and 3,4675 mg amlodipine besilate equivalent to 2,5 mg amlodipine.

Excipient with known effect 31,62 mg lactose monohydrate.

Viacoram 7/5 mg tablets

One tablet contains 4,756 mg perindopril equivalent to 7 mg perindopril arginine and 6,935 mg amlodipine besilate equivalent to 5 mg amlodipine.

Excipient with known effect 63.23 mg lactose monohydrate.

Viacoram 14/10 mg tablets

One tablet contains 9,512 mg perindopril equivalent to 14 mg perindopril arginine and 13,870 mg amlodipine besilate equivalent to 10 mg amlodipine.

Excipient with known effect 126,48 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Viacoram 3,5/2,5 mg White, round tablet, 5 mm diameter.

Viacoram 7/5 mg White, round tablet, 6 mm diameter, engraved with  on one face.

Viacoram 14/10 mg White, round tablet, 8 mm diameter, engraved with

14/10 on one face and  on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Viacoram is indicated for the treatment of essential hypertension in adults.

4.2 Posology and method of administration

Posology

For oral administration.

Viacoram should be taken as a single dose, preferably in the morning and before a meal.

Viacoram 3,5/2,5 mg is intended for first line therapy in patients with arterial hypertension.

The recommended starting dose of Viacoram is 3,5/2,5 mg once daily.

After at least four weeks of treatment, the dose may be increased to 7/5 mg once daily in patients whose blood pressure is not adequately controlled with Viacoram 3,5/2,5 mg.

If necessary, titration to 14/10 mg once daily may be considered in adult patients insufficienltey controlled after four weeks of treatment with 7/5 mg.

Special populations

Patients with renal impairment (see sections 4.3, 4.4 and 5.2)

Viacoram is contraindicated in patients with severe renal impairment (Creatinine clearance below 30 ml/min) (see section 4.3).

In patients with moderate renal impairment (Creatinine clearance between 30 ml/min to 60 ml/min), the initial recommended dose of Viacoram is 3,5/2,5 mg every other day. In patients whose blood pressure is not adequately controlled, the dose of Viacoram 3,5/2,5 mg may be taken once daily. If necessary, the dose may be increased in patients insufficiently controlled. Medical follow-up includes monitoring of creatinine and potassium (see sections 4.4 and 5.2).

Patients with hepatic impairment (see sections 4.4 and 5.2)

Caution should be exercised when prescribing Viacoram to patients with severe hepatic impairment.

Elderly patients (≥ 65 years of age) (see sections 4.4 and 5.2)

Caution is advise with the treatment of elderly patints. Renal function should be cehcked before initaiting treatment.

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After initiation of the treatment, renal function should be monitored before increase of the dosage, particularly in patients aged 75 years and above. The usual medical follow-up should include monitoring of creatinine and potassium.

Paediatric population

The safety and efficacy of Viacoram in children aged below 18 years have not been established. No data are available.

4.3 Contraindications

- Hypersensitivity to the active substances, to ACE-inhibitors, to dihydropyridines derivatives, or to any of the excipients listed in section 6.1.
- Severe renal function impairment (creatinine clearance less than 30 ml/min) (see sections 4.2 and 4.4).
- History of angioedema associated with previous ACE-inhibitor therapy or angiotensin receptor blockers (ARBs): These patietns must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructiuve cardiomyopathy (HOCM).
- Severe hypotension.
- Concomitant therapy with potassium sparing diuretics suchas sprironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- Haemodynamically unstable heart failure after acute myocardial infarction.
- Concomitant use of Viacoram with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73 m^2) (see sections 4.5 and 5.1).
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).
- Significant bilateral renal artery stenosis.
- Renal artery stenosis in a single functioning kidney (see section 4.4).
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.

- Concomitant use with sacubitril/valsartan therapy, Perindopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5).
- Pregnancy and lactation (see section 4.6).
- Lithium therapy: Concomitant administration with Viacoram may lead to toxic lithium blood concentrations (see section 4.5).
- Concomitant use of Viacoram with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73m²) (see sections 4.4, 4.5 and 5.1).
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).
- 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.

Linked to amlodipine

- Severe hypotension
- Hypersensitivity to amlodipine, or dihydropyridine derivatives.
- Shock (including cardiogenic shock).
- Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.
- Severe impairment of hepatic function (Child Pugh C).

4.4 Special warnings and precautions for use

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

Special warnings

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx with difficult breathing has been reported in patients treated with ACE-inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy**.** In such cases, Viacoram should promptly be discontinued and appropriate management and monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of epinephrine (adrenaline) and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving Viacoram (see section 4.3).

Intestinal angioedema has been reported in patients treated with ACE-inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE-inhibitor. Intestinal angioedema should be included

in the differential diagnosis of patients on ACE-inhibitors presenting with abdominal pain (see section 4.8).

The combination of perindopril with **sacubitril/valsartan** is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE-inhibitors with NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE-inhibitor.
Careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Patients receiving ACE-inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE- inhibitor therapy prior to each apheresis.

Anaphylactoid reactions during desensitisation

Patients receiving ACE-inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been

avoided when the ACE-inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high flux membranes and treated concomitantly with an ACE-inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors. Viacoram should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Viacoram is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

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

There is evidence that the concomitant use of ACE-inhibitors such as Viacoram, 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.

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 angiotensin II receptor blockers should not be used

concomitantly in patients with diabetic nephropathy. Viacoram should not be used concomitantly with aliskiren (see sections 4.3 and 4.5).

Concomitant use of 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.

Primary aldosteronism

Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of Viacoram is not recommended.

Use in patients with renal impairment

Viacoram is contraindicated in patients with severe renal impairment (Creatinine clearance below 30 ml/min) (see section 4.3).

In patients with moderate renal impairment (Creatinine clearance between 30 ml/min to 60 ml/min), the initial recommended dose of Viacoram is 3,5/2,5 mg every other day (see section 4.2). Medical follow-up in such patients should include monitoring of potassium levels and creatinine (see sections 4.2 and 5.2).

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE-inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. Some hypertensive patients with

no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment.

Amlodipine may be used in patients with renal failure at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Kidney transplantation

Since there is no experience regarding the administration of Viacoram in patients with a recent kidney transplantation, treatment with Viacoram is therefore not recommended.

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE-inhibitors (see section 4.3). Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only minor changes in serum creatinine even in patients with unilateral renal artery stenosis.

Use in patients with impaired hepatic function

Rarely, ACE-inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Viacoram who develop jaundice or marked elevations of hepatic enzymes should discontinue Viacoram and receive appropriate medical follow-up (see section 4.8).

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function.

Elderly patients (≥ 65 years of age)

Initiation and increase of the dosage should take place with care in older people, depending on renal function.

Renal function should be monitored before increase of the dosage. Therefore, the medical follow-up should include monitoring of potassium and creatinine (see sections 4.2 and 5.2).

Precautions for use

Hypertensive crisis

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

Use in patients with cardiac failure

Patients with heart failure should be treated with caution.

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

Hypotension

ACE-inhibitors may cause a fall in blood pressure. Symptomatic hypotension has been reported in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients at high risk of symptomatic hypotension, blood pressure, renal function and serum potassium should be monitored frequently during treatment with Viacoram.

Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0,9 %) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

ACE-inhibitors should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy (see section 4.3).

Race

ACE-inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

ACE-inhibitors may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

Cough

Cough has been reported with the use of Viacoram. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with medicines that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. Viacoram should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia

Elevations in serum potassium have been observed in patients treated with ACE-inhibitors, including perindopril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride, alone or in combination), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin, other ACE-inhibitors, angiotensin-II antagonists, acetylsalicylic acid ≥ 3 g/day, COX-2 inhibitors and non-selective NSAIDs, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and fixed dose combination with sulfamethoxazole (co-trimoxazole). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal dysrhythmia. If concomitant use of Viacoram and any of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with Viacoram (see section 4.5).

The combination of Viacoram and potassium-sparing medicines, potassium supplements or potassium-containing salt substitutes is not recommended (see section 4.5).

Excipients

Viacoram contains lactose. Patients with rare hereditary problems of galactose intolerance (e.g. galactocaemia), the total lactase deficiency or glucose-galactose malabsorption should not take Viacoram.

4.5 Interaction with other medicines and other forms of interaction

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

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 (including acute renal failure) compared to the use of a single RAAS-acting medicine (see sections 4.3, 4.4 and 5.1).

Medicines increasing the risk of angioedema

Concomitant use of ACE-inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use of ACE-inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk for angioedema (see section 4.4).

Medicines inducing hyperkalaemia

Some medicines or therapeutic classes may increase the occurrence of hyperkalaemia such as aliskiren, potassium salts, potassium-sparing diuretics, ACE-inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant medicines such as ciclosporin or tacrolimus, trimethoprim and fixed dose combination with sulfamethoxazole (Co-trimoxazole). The combination of Viacoram with these medicines increases the risk of hyperkalaemia (see

section 4.4). The combination of Viacoram with the above-mentioned medicines is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Concomitant use contraindicated (see section 4.3)

Fluoroquinolones

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).

Aliskiren

In patients with diabetes mellitus or with impaired renal function, the risk of hyperkalaemia, deterioration of renal function, and cardiovascular morbidity and mortality are increased.

Extracorporeal treatments

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate should be avoided due to an increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

NEP inhibitors

The concomitant use of perindopril with sacubitril/valsartan is contraindicated, as the concomitant inhibition of neprilysin (NEP) and ACE may increase the risk of angioedema.

Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4). Concomitant use of other NEP inhibitors (e.g. racecadotril) and perindopril may also increase the risk of angioedema (see section 4.4).

Concomitant use not recommended (see section 4.4)

Estramustine

There is a risk of increased adverse effects such as angioneurotic oedema (angioedema).

Potassium-sparing diuretics (e.g. triamterene, amiloride), potassium (salts)

Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). ACE-inhibitors must not be used with hyperkalaemic substances, except in hypokalaemia.

The combination of Viacoram with the above-mentioned medicines is not recommended (see section 4.4). If concomitant use is nonetheless indicated, they should be with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see below.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE-inhibitors. Use of Viacoram with lithium is contraindicated (see section 4.3).

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse occurred in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of Viacoram containing

amlodipine, a calcium channel blocker, be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Concomitant use which requires special care

Antidiabetic agents (insulins, oral hypoglycaemic agents)

Concomitant administration of ACE-inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Baclofen

Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

Non-potassium-sparing diuretics

Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE-inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating Viacoram.

In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, the diuretic must be discontinued before initiating Viacoram , in which case a non-potassium-sparing diuretic can be thereafter reintroduced.

Renal function (creatinine levels) must be monitored during the first few weeks of Viacoram therapy.

Potassium-sparing diuretics (eplerenone, spironolactone)

With the use of eplerenone or spironolactone at doses between 12,5 mg to 50 mg per day and with low doses of ACE-inhibitors for the treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40 %, and previously treated with ACE-inhibitors and loop diuretics, there is a risk of hyperkalaemia, which may be fatal , especially with non adherence to the recommendations for use of Viacoram. .

Before initiating the combination, check for the absence of hyperkalaemia and renal impairment.

Frequent monitoring of the potassium and creatinine should be done. in the first month of treatment, at least once a week at the beginning of treatment and then monthly thereafter.

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥ 3 g/day

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of Viacoram and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function before initiation of concomitant therapy, and frequently thereafter.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE-inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE-inhibitors with heparin. Monitoring of serum potassium is recommended.

Racecadotril

ACE inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a drug used against acute diarrhea) (see section 4.4).

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

Gliptins (*e.g.* linagliptin, saxagliptin, sitagliptin, vildagliptin)

Increased risk of angio-oedema, due to dipeptidyl peptidase IV (DPP-IV) decreased activity by the gliptin, in patients co-treated with an ACE inhibitor.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

CYP3A4 inhibitors

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 PK

variations may be more pronounced in the elderly. Clinical monitoring and Viacoram dose adjustment may thus be required.

There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co administered with clarithromycin.

Concomitant use which requires some care

Antihypertensive medicines (such as beta-blockers) and vasodilators

Concomitant use of these medicines may increase the hypotensive effects of Viacoram. Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.

Tricyclic antidepressants/Antipsychotics/Anaesthetics

Concomitant use of certain anaesthetic medicines , tricyclic antidepressants and antipsychotics with Viacoram may result in further reduction of blood pressure.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of Viacoram .

Corticosteroids, tetracosactide

Concomitant use of Viacoram with corticosteroids or tetracosactide may reduce the antihypertensive effect of Viacoram due to the salt and water retention properties of corticosteroids.

Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin)

Increased antihypertensive effect and increased risk of orthostatic hypotension.

Amifostine

May potentiate the antihypertensive effect of amlodipine.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE-inhibitor therapy including perindopril.

Grapefruit

Administration of Viacoram with grapefruit or grapefruit juice is not recommended as amlodipine bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Ciclosporin

No drug interaction studies have been conducted with ciclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable

trough concentration increases (average 0 % - 40 %) of ciclosporin were observed. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on amlodipine, and ciclosporin dose reductions should be made as necessary.

4.6 Pregnancy, fertility and lactation

Viacoram is contraindicated in pregnancy and lactation.

Pregnancy

Linked to perindopril

The use of Viacoram contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take Viacoram during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Viacoram should be stopped immediately and alternative therapy should be started.

Foetal exposure to ACE-inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spina bifida) and of kidney malformations.

Viacoram passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in new-borns, have been reported after administration of Viacoram during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Linked to amlodipine

Amlodipine should not be used in pregnancy as the safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses.

Breastfeeding

Linked to perindopril

Women on treatment with perindopril should not breastfeed their babies. No information is available regarding the use of perindopril during breastfeeding.

Linked to amlodipine

Women on treatment with amlodipine should not breastfeed their babies. Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7 %, with a maximum of 15 %. The effect of amlodipine on infants is unknown. .

Fertility

Linked to perindopril

There was no effect on reproductive performance or fertility in animal studies.

Linked to amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Perindopril and amlodipine influence the ability to drive and use machines. Patients should not drive and use machines until they know how treatment with Viacoram affects them. If patients suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired.

Caution is recommended with Viacoram especially at the start of treatment.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Viacoram has been evaluated on a 6-month controlled study involving 1 771 patients, 887 of whom received Viacoram, a 6-week controlled study involving 837 patients, 279 of whom received Viacoram, and an 8-week placebo-controlled study involving 1 581 patients, 249 of whom received Viacoram .

In these clinical studies, no significant new adverse reactions were observed with the combination compared to the known effects of the individual monocomponents.

The following adverse reactions were found to be the most frequently reported during clinical trials dizziness, cough and oedema.

The adverse drug reactions previously reported during clinical trials and/or post-marketing experience with one of the individual components of Viacoram (perindopril and amlodipine) have been listed in the following table since they may occur with the fixed-dose combination.

List of adverse reactions reported during clinical trials

The following undesirable effects have been observed during clinical trials treatment with Viacoram , perindopril or amlodipine given separately and ranked under the MedDRA classification by body system and under the following frequency

Very common (≥ 1/10) ; common (≥ 1/100 to < 1/10) ; uncommon (≥ 1/1 000 to < 1/100) ; rare (≥ 1/10 000 to < 1/1 000) ; very rare (< 1/10 000) ; not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Viacoram (Perindopril/ Amlodipine)	**Amlodipine**	**Perindopril**
Infections and infestations	Rhinitis	-	Uncommon	Very rare
Blood and the lymphatic System Disorders				
		-	Very rare	Very rare
	Agranulocytosis or pancytopenia (see section 4.4)	-	-	Very rare
	Leukopenia/neutropenia (see section 4.4)	-	Very rare	Very rare
	Haemolytic anaemia enzyme specific in patients with a congenital deficiency of G-6PDH (see section 4.4)	-	-	Very rare
Immune System Disorders	Hypersensitivity	-	Very rare	Uncommon
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	-	-	Rare
Metabolism and Nutrition Disorders	Hyperkalaemia (see section 4.4)	Uncommon	-	

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**		
		Viacoram (Perindopril/ Amlodipine)	**Amlodipine**	**Perindopril**
	Hyperglycaemia	Uncommon	Very rare	-
Psychiatric Disorders	Mood altered (including anxiety)	-	Uncommon	Uncommon
	Insomnia	-	Uncommon	-
	Depression	-	Uncommon	Uncommon*
	Sleep disorder	-	-	Uncommon
	Confusional state		Rare	Very rare
Nervous System Disorders	Dizziness (especially at the beginning of the treatment)	Common	Common	Common
	Headache (especially at the beginning of the treatment)	-	Common	Common
	Somnolence (especially at the beginning of the treatment)	-	Common	-
	Dysgeusia	-	Uncommon	Common
	Paraesthesia		Uncommon	Common
	Syncope	-	Uncommon	-
	Hypoaesthesia	-	Uncommon-	-
	Tremor	-	Uncommon	-
	Hypertonia	-	Very rare	-
	Neuropathy peripheral	-	Very rare	-

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Viacoram (Perindopril/ Amlodipine)	**Amlodipine**	**Perindopril**
	Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	-	Very rare
	Extrapyramidal disorder (extrapyramidal syndrome)	-	Not known	-
Eye Disorders	Visual impairment	-	Common	Common
	Diplopia	-	Common	-
Ear and labyrinth Disorders	Tinnitus	-	Uncommon	Common
	Vertigo	-	-	Common
Cardiac Disorders	Palpitations	-	Common	
	Tachycardia	-	-	Uncommon*
	Angina pectoris	-	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	-	Very rare	Very rare
	Dysrhythmias (including bradycardia, ventricular tachycardia and atrial fibrillation)	-	Uncommon	Very rare
Vascular Disorders	Flushing	-	Common	Rare*

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Viacoram (Perindopril/ Amlodipine)	**Amlodipine**	**Perindopril**
	Hypotension (and effects related to hypotension)	-	Uncommon	Common
	Vasculitis	-	Very Rare	-
	Raynaud's phenomenon	-	-	Not known
Respiratory, Thoracic and Mediastinal Disorders	Cough	Common	Uncommon	Common
	Dyspnoea	-	Common	Common
	Bronchospasm	-	-	Uncommon
	Eosinophilic pneumonia	-	-	Very rare
Gastro-intestinal Disorders	Abdominal pain	-	Common	Common
	Nausea	-	Common	Common
	Vomiting	-	Uncommon	Common
	Dyspepsia	-	Common	Common
	Diarrhoea	-	Common	Common
	Constipation	-	Common	Common
	Change of bowel habit	-	Common	-
	Dry mouth	-	Uncommon	Uncommon
	Gingival hyperplasia	-	Very rare	-

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Viacoram (Perindopril/ Amlodipine)	**Amlodipine**	**Perindopril**
	Pancreatitis	-	Very rare	Very rare
	Gastritis	-	Very rare	-
Hepato-biliary Disorders	Hepatitis, jaundice	-	Very rare	-
	Hepatitis either cytolytic or cholestatic (see section 4.4)	-	-	Very rare
Skin and Subcutaneous Tissue Disorders	Rash, exanthema	-	Uncommon	Common
	Pruritus	-	Uncommon	Common
	Hyperhidrosis	-	Uncommon	Uncommon
	Alopecia	-	Uncommon	-
	Purpura	-	Uncommon	-
	Skin discolouration	-	Uncommon	-
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)	-	Very rare	Uncommon
	Urticaria	-	Uncommon	Uncommon
	Photosentivity reaction	-	Very rare	
	Erythema multiforme	Uncommon	Very rare	Very rare

MedDRA System Organ Class	Undesirable Effects	Frequency		
		Viacoram (Perindopril/ Amlodipine)	**Amlodipine**	**Perindopril**
	Quincke's oedema	-	Very rare	-
	Stevens-Johnson Syndrome	-	Very rare	-
	Exfoliative dermatitis	-	Very rare	-
	Toxic Epidermal Necrolysis	-	Not known	-
	Psoriasis aggravation	-	-	Rare
Musculoskeletal And Connective Tissue Disorders	Back pain	-	Uncommon	-
	Joint swelling (ankle swelling)		Common	-
	Muscle spasms	-	Common	Common
	Arthralgia, myalgia	-	Uncommon	
Renal and Urinary Disorders	Micturition disorder, nocturia, pollakiuria	-	Uncommon	-
	Renal failure	-	-	Uncommon
	Acute renal failure	-	-	Rare
	Anuria/Oliguria	-	-	Rare*
Reproductive System and Breast Disorders	Erectile dysfunction	-	Uncommon	Uncommon

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**		
		Viacoram (Perindopril/ Amlodipine)	**Amlodipine**	**Perindopril**
	Gynaecomastia	-	Uncommon	-
General Disorders and Administration Site Conditions	Oedema peripheral	Common	-	-
	Oedema	-	Very common	-
	Fatigue	Uncommon	Common	-
	Asthenia	-	Common	Common
	Chest pain	-	Uncommon	-
	Malaise	-	Uncommon	-
	Pain	-	Uncommon	-
Investigations	Weight increased, weight decreased	-	Uncommon	-
	Blood bilirubin increased	-	-	Rare
	Hepatic enzyme increased	-	Very rare	Rare
	Haemoglobin decreased and haematocrit decreased	-	-	Very rare

The following adverse events were reported during post marketing use:

Blood and the lymphatic system disorders	Eosinophilia
Metabolism and nutrition disorders	Hyperkalaemia (see section 4.4), Hyponatraemia, Hypoglycaemia (see sections 4.4 and 4.5)
Nervous system disorders	Somnolence (especially at the beginning of the treatment), Syncope
Cardiac disorders	Palpitations, Tachycardia
Vascular disorders	Vasculitis
Skin and subcutaneous tissue disorders	Pemphigoid, Photosensitivity reaction
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia
General disorders and administration site conditions	Oedema peripheral, Chest pain, Malaise, Pyrexia
Investigations	Blood urea increased, Blood creatinine increased
Injury, poisoning and procedural complications	Fall

Additional information on the combination perindopril/amlodipine

A randomised, double-blind, placebo-controlled study over 8 weeks demonstrated that peripheral oedema, a recognised side effect of amlodipine, was observed at a lower incidence in patients who received the perindopril 3,5mg/amlodipine 2,5 mg combination than in those who received amlodipine 5 mg alone (1,6 % and 4,9 % respectively).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of Viacoram is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug**

Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no experience of overdose with Viacoram .

For amlodipine, experience with intentional overdose in humans is limited.

Symptoms available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24 - 48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory 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.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

For perindopril, limited data are available for overdosage in humans. Symptoms associated with the overdosage of ACE-inhibitors may include hypotension, circulatory shock, electrolyte

disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdosage is intravenous infusion of 0,9 % sodium chloride solution. If hypotension occurs, the patient should be placed in the shock position (patient to lie on their back with legs elevated above heart level). If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril can be removed from the systemic circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for treatment-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group medicines acting on the renin-angiotensin system, ACE-inhibitors and calcium channel blockers, ATC code C09BB04.

Mechanism of action

Viacoram combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension. Amlodipine belongs to the calcium antagonist class and perindopril to the angiotensin converting enzyme inhibitors class of medicines.

The combination of these substances has an additive antihypertensive effect.

Pharmacodynamic effects

Perindopril

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing

the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE-inhibitors and is partially responsible for certain of their side effects (e.g. cough).

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro.

Amlodipine

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx 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.

- Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
- The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions.

5.2 Pharmacokinetic properties

The rate and extent of absorption of perindopril and amlodipine from Viacoram are not significantly different, respectively, from the rate and extent of absorption of perindopril and amlodipine from individual tablet formulations.

Perindopril

Absorption

After oral administration, perindopril is well absorbed and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Distribution

The volume of distribution is approximately 0,2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20 %, principally to angiotensin converting enzyme, but is concentration-dependent.

Elimination

Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days.

Amlodipine

Absorption, distribution, plasma protein binding

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80 %. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97,5 % of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation, elimination

The terminal plasma elimination half-life is about 35 - 50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10 % of the parent compound and 60 % of metabolites excreted in the urine.

Special populations

Paediatric population (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

The elderly population (≥ 65 yeasrs of age)

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients.

Initiation and increase of the dosage should take place with care in elderly people depending on renal function.

Elimination of perindoprilat is decreased in the elderly. Renal function should be monitored before increase of the dosage. Therefore, medical follow-up will include monitoring of creatinine and potassium (see sections 4.2 and 4.4).

Renal impairment

In patients with moderate renal impairment (Creatinine clearance between 30 ml/min to 60 ml/min), the initial recommended dose of Viacoram is 3,5/2,5 mg every other day (see section 4.2).

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Amodipine is not dialysable.

Elimination of perindoprilat is decreased in patients with heart or renal failure.

Therefore, medical follow-up will include monitoring of creatinine and potassium (see sections 4.2 and 4.4).

Hepatic impairment

Caution should be exercised in patients with liver disease (see sections 4.2 and 4.4).

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40 – 60 %.

Dialysis clearance of perindoprilat is equal to 70 ml/min. Perindopril kinetics are modified in patients with cirrhosis hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required (see sections 4.2 and 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.

Cellulose, microcrystalline (E460).

Silica, colloidal anhydrous (E551).

Magnesium stearate (E470B).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Tablet container of 30 tablets Once opened, Viacoram should be used within 30 days.

6.4 Special precautions for storage

Store at or below 30 ºC.

Keep out of reach of children.

Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

30 tablets in polypropylene tablet container equipped with a low density polyethylene stopper containing a desiccant gel (silica) and a low density polyethylene flow reducer.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTATION

Servier Laboratories SA (Pty) Ltd

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Hertford Office Park

90 Bekker Road

Vorna Valley

Midrand

2169

REGISTRATION NUMBERS

Viacoram 3,5/2,5 mg tablets: 52/7.1.3/0709

Viacoram 7/5 mg tablets: 52/7.1.3/0710

Viacoram 14/10 mg tablets: 52/7.1.3/0711

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

4 May 2021

10. DATE OF REVISION OF TEXT

19 April 2023