APPROVED SPC

For

MIXANVAL

Registration No.:

Mixanval 5 mg/5 mg tablets 43/7.1.3/0937
Mixanval 5 mg/10 mg tablets 43/7.1.3/0938
Mixanval 10 mg/5 mg tablets 43/7.1.3/0939
Mixanval 10 mg/10 mg tablets 43/7.1.3/0940

Date Approved: April 2020

Confidential Information

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Approved PI	
Applicant	Servier Laboratories SA (Pty) Ltd
Product	**Mixanval** tablets
Approval date	17 April 2020

Mixanval

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

Mixanval 5 mg/5 mg tablets.

Mixanval 5 mg/10 mg tablets.

Mixanval 10 mg/5 mg tablets.

Mixanval 10 mg/10 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mixanval 5 mg/5 mg tablets: One tablet contains 5 mg perindopril arginine and 5 mg amlodipine (as amlodipine besilate).

Mixanval 5 mg/10 mg tablets: One tablet contains 5 mg perindopril arginine and 10 mg amlodipine (as amlodipine besilate).

Mixanval 10 mg/5 mg tablets: One tablet contains 10 mg perindopril arginine and 5 mg amlodipine (as amlodipine besilate).

Mixanval 10 mg/10 mg tablets: One tablet contains 10 mg perindopril arginine and 10 mg amlodipine (as amlodipine besilate).

3. PHARMACEUTICAL FORM

Mixanval 5 mg /5 mg tablets White, rod-shaped tablet engraved with 5/5 on one face and  on the other face.

Mixanval 5 mg/10 mg tablets: White, square-shaped tablet engraved with 5/10 on one face and on the other face.

Mixanval 10 mg/5 mg tablets: White triangular-shaped tablet engraved with 10/5 on one face and on the other face.

Mixanval 10 mg/10 mg tablets: White round tablet engraved with 10/10 on one face and  on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mixanval is indicated for the treatment of hypertension in patients already stabilised with perindopril and amlodipine at equivalent dosages.

Treatment of hypertension in patients uncontrolled on either perindopril or amlodipine monotherapy.

4.2 Posology and method of administration

Posology

For oral administration. One tablet per day as a single dose, preferably to be taken in the morning before breakfast. The fixed dose combination is not suitable for initiation therapy.

If a change in dose is required, the dose of **Mixanval** should be modified.

Special populations

Patients with renal impairment and elderly (see section 4.4) Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium. **Mixanval** can be administered in patients with $Cl_{cr} \geq 60$ ml/min, and is not suitable for patients with Cl_{cr} < 60 ml/min. In these patients, an individual dose titration with the mono-components is recommended. Normal dosage regimens are recommended in the elderly. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. Amlodipine is not dialysable.

Patients with hepatic impairment (see sections 4.4 and 5.2) Dosage recommendations have not been established in patients with mild to moderate

hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2) To find the optimal starting dose and maintenance dose of patients with hepatic impairment, the patients should be individually titrated using the free combination of amlodipine and perindopril. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Paediatric population

Mixanval should not be used in children and adolescents as the efficacy and tolerability of perindopril and amlodipine, in combination, have not been established in children and adolescents.

4.3 Contraindications

Linked to perindopril

- Hypersensitivity to any of the ingredients of **Mixanval**
- A history of angioedema related to previous therapy with ACE-inhibitors or angiotensin receptor blockers (ARBs). These patients must never again be given these medicines. (see section 4.4)
- Hereditary or idiopathic angioedema (see section 4.4)
- Hypertrophic obstructive cardiomyopathy (HOCM) (see section 4.4)
- Severe renal function impairment (creatinine clearance less than 30 ml/min) (see sections 4.2 and 4.4)
- Bilateral renal artery stenosis (see section 4.4)
- Renal artery stenosis in patients with a single kidney (see section 4.4)
- Aortic stenosis (see section 4.4)

- Concomitant therapy with potassium-sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5)
- Porphyria
- Lithium therapy Concomitant use with **Mixanval** may lead to toxic blood concentration of lithium (see section 4.5)
- Pregnancy and lactation (see section 4.4 and 4.6)
- The concomitant use of **Mixanval** with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73 m^2) (see sections 4.4 and 4.5)
- Concomitant use with sacubitril/valsartan (see sections 4.4 and 4.5)

  Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4)
- Concomitant use of fluoroquinolones with ACE-inhibitors/Renin angiotensin receptor blockers is contraindicated in patients with moderate to severe renal failure (creatinine clearance ≤ 30 ml/min) and in elderly patients.

Linked to amlodipine

- Hypersensitivity to amlodipine or to dihydropyridines derivatives
- Severe hypotension
- 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.

Linked to Mixanval

All contraindications related to each mono-component, as listed above, should apply also to the fixed combination of **Mixanval**.

- Hypersensitivity to any of the excipients.

4.4 Special warnings and precautions for use

Special warnings

All warnings related to each mono-component, as listed below, should apply also to the fixed combination of **Mixanval.**

Linked to perindopril

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

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **Mixanval** and aliskiren is therefore contraindicated (see section 4.3). **Mixanval** should not be used concomitantly with aliskiren (see section 4.3).

Hypersensitivity/Angioedema

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx 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, **Mixanval** should promptly be discontinued and appropriate 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 patient's 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 **Mixanval** (see section 4.3). Intestinal angioedema has been reported in patients treated with ACE-inhibitors such as in **Mixanval**. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there were 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 **Mixanval** 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 other **NEP inhibitors** (e.g. racecadotril) and ACE-inhibitors may also increase the risk of angioedema (see section 4.5). A careful benefit-risk assessment is needed before initiating treatment with NEP inhibitors (e.g. racecadotril) in patients on perindopril.

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment (see section 4.5).

Anaphylactic reactions during low-density lipoproteins (LDL) apheresis

Patients receiving perindopril, as in **Mixanval** 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.

Anaphylactic 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.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors. In patients with normal renal function and no other complicating factors, neutropenia rarely occurs. **Mixanval** 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 not always responded to intensive antibiotic therapy. If perindopril 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).

Renovascular hypertension

There is an increased risk of hypotension and renal insufficiency when patient 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.

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 **Mixanval** is not recommended.

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE-inhibitors/Renin 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/Renin angiotensin receptor blockers whether used separately and/or concomitantly.

Precautions for use

Hypotension

ACE-inhibitors may cause a fall in blood pressure. Symptomatic hypotension is rarely seen 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 closely during treatment with **Mixanval.**

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 usually be given without difficulty once the blood pressure has increased after volume expansion.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

Mixanval should be administered with caution to patients with mitral valve stenosis.

Mixanval is contraindicated in patients with obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy. (see section 4.3).

Renal impairment

In cases of renal impairment (creatinine clearance < 60 ml/min) an individual dose titration with the mono-components is recommended (see section 4.2). Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8).

Mixanval is contraindicated in patients with bilateral renal artery stenosis, or stenosis of the artery to a solitary kidney due to an increased risk of renal function impairment. In patients treated with **Mixanval**, increases in blood urea and serum creatinine may occur.

This is usually reversible upon discontinuation of therapy. It 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.

Hepatic failure

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 **Mixanval** who develop jaundice or marked elevations of hepatic enzymes should discontinue **Mixanval** and receive appropriate medical follow-up (see section 4.8).

Race

ACE-inhibitors cause a higher rate of angioedema in black patients than in non-black patients. **Mixanval** 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 commonly with the use of ACE-inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. **Mixanval** induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia

In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, **Mixanval** may block angiotensin II formation secondary to compensatory renin release. The treatment 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 **Mixanval**. Risk factors for the development of hyperkalaemia 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), potassium supplements or potassium-containing salt substitutes; or those

patients taking other medications associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). 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. Hyperkalaemia can cause serious, sometimes fatal dysrhythmias. (see sections 4.3 and 4.5). If concomitant use of perindopril 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 an ACE-inhibitor (see section 4.5).

Linked to amlodipine

Precautions for use

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.

In a long-term, placebo-controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. 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.

Use in patients with impaired hepatic function

The half-life of amlodipine is prolonged, and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Individual titration with the free combination should be done before the patient is switched back to **Mixanval** (fixed dose combination). Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Use in elderly patients

In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.1).

Use in renal failure

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

Linked to Mixanval

All warnings related to each monocomponent, as listed above, should apply also to the fixed combination of **Mixanval.**

Precautions for use

Excipients

Mixanval tablets contain lactose.

Patients with rare hereditary problems of galactose intolerance e.g. galactasaemia, Lapp lactase deficiency, or glucose-galactose malabsorption or fructose intolerance should not take **Mixanval**.

Interactions

The concomitant use of **Mixanval** with lithium, potassium-sparing diuretics or potassium supplements, or dantrolene is contraindicated (see sections 4.3 and 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Linked to perindopril

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).

Medicines inducing hyperkalaemia

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

Concomitant use contraindicated (see section 4.3)

Aliskiren

In diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

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 s ulphate due to 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.

Sacubitril/valsartan

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 the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after taking the last dose of sacubitril/valsartan. (see sections 4.3 and 4.5).

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE-inhibitors/Renin 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).

Concomitant use not recommended (see section 4.4).

Aliskiren

In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase.

Concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker

It has been reported in the literature that in patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g, by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure.

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

Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects).

The combination of perindopril with the above-mentioned medicines is not recommended **(**see section 4.4). If the concomitant use is indicated because of documented hypokalaemia, it should be cautiously and with frequent monitoring of potassium. For use of spironolactone in heart failure, see below.

Lithium

Reversible increases in serum lithium concentrations and toxicity (severe neurotoxicity) have been reported during concurrent use of ACE-inhibitors. The combination of **Mixanval** with lithium is contraindicated (see section 4.3).

Estramustine

Risk of increased adverse effects such as angioedema.

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients concomitantly taking co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia see section 4.4).

Concomitant use which requires special care

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 **Mixanval** 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 after initiation of concomitant therapy, and periodically thereafter.

Antidiabetic agents (insulin, oral hypoglycaemic agents)

Epidemiological studies have suggested that 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.

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 **Mixanval**. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of **Mixanval**.

In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE-inhibitor, in

which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE-inhibitor must be initiated with a low dosage and progressively increased.

In diuretic-treated congestive heart failure, the ACE-inhibitor should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic. In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE-inhibitor therapy.

Potassium-sparing diuretics (eplerenone, spironolactone)

With eplerenone or spironolactone at doses between 12,5 mg to 50 mg by day and with low doses of ACE-inhibitors

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40 % and previously treated with ACE-inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.

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

A close monitoring of the potassium and creatinine is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Racecadotril

ACE-inhibitors (e.g. perindopril) are known to cause angioedema. This risk may be elevated when used concomitantly with racecadotril (a medicine used against acute diarrhoea).

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

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

Concomitant use which requires some care

Gliptines (linagliptin, saxagliptin, sitagliptin, vildagliptin)

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

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of **Mixanval.**

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 **Mixanval**.

Linked to amlodipine

Concomitant use not recommended

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 co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Concomitant use which requires special care

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 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 to be taken into consideration

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

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.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Other concomitant use

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin.

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

Linked to Mixanval

All of the above and in addition

Concomitant use which requires special care

Baclofen

Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

Concomitant use to be taken into consideration

Antihypertensive agents (such as beta-blockers) and vasodilators

Concomitant use of these agents may increase the hypotensive effects of **Mixanval**.

Concomitant use with nitroglycerine, other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.

Corticosteroids, tetracosactide

Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

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

Increased antihypertensive effect and an increased risk of orthostatic hypotension.

Amifostine

May potentiate the antihypertensive effect of amlodipine contained in **Mixanval**.

Tricyclic antidepressants / antipsychotics / anaesthetics

Increased antihypertensive effect and an increased risk of orthostatic hypotension.

4.6 Fertility, pregnancy and lactation

Pregnancy

Linked to perindopril

The use of **Mixanval** is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take **Mixanval** 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 **Mixanval** should be stopped immediately and if appropriate, 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.

Mixanval 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 newborns, have been reported after administration of **Mixanval**, 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

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is not recommended.

Lactation

Linked to perindopril

Because no information is available regarding the use of perindopril during lactation, perindopril is contraindicated.

Linked to amlodipine

Safety of amlodipine during lactation has not been established. It is not known whether amlodipine is excreted in breast milk.

Fertility

Linked to perindopril

There was no effect on reproductive performance or fertility.

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.

4.7 Effects on ability to drive and use machines

No studies on the effects of **Mixanval** on the ability to drive and use machines have been performed. Caution is advised as amlodipine can influence the ability to drive and use machines. If patients suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired.

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse reactions with perindopril and amlodipine given separately are oedema, somnolence, dizziness, headache (especially at the beginning of the treatment), dysgeusia, paraesthesia, visual impairment (including diplopia), tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), dyspnoea, cough, abdominal pain, nausea, vomiting, dyspepsia, change of bowel habit, diarrhoea, constipation, pruritis, rash, exanthema, joint swelling (ankle swelling), muscle spasms, fatigue, asthenia.

The following side effects have been observed during treatment with 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).

System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	**Perindopril**
Infections and infestations	Rhinitis	Uncommon	Very rare
Blood and lymphatic System Disorders	Eosinopilia	-	Uncommon*
	Leucopenia/neutropenia (see section 4.4)	Very rare	Very rare
	Agranulocytosis or pancytopenia (see section 4.4)	-	Very rare
	Thrombocytopenia (see section 4.4)	Very rare	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)	-	Very rare
Immune System Disorders	Hypersensitivity	Very rare	Uncommon
Metabolism and Nutrition Disorders	Hyperglycaemia	Very rare	-
	Hypoglycaemia (see sections 4.4 and 4.5)	-	Uncommon*
	Hyperkalaemia, reversible on discontinuation (see section 4.4)	-	Uncommon*
	Hyponatraemia	-	Uncommon*
Psychiatric disorders	Insomnia	Uncommon	-
	Mood changes (including anxiety)	Uncommon	Uncommon
	Depression	Uncommon	-
	Sleep disturbances	-	Uncommon
Nervous System disorders	Somnolence (especially at the beginning of the treatment)	Common	Uncommon*
	Dizziness (especially at the beginning of the treatment)	Common	Common

System Organ Class	Undesirable Effects	Frequency	
		Amlodipine	**Perindopril**
	Headache (especially at the beginning of the treatment)	Common	Common
	Dysgeusia	Uncommon	Common
	Tremor	Uncommon	-
	Hypoaesthesia	Uncommon	-
	Paraesthesia	Uncommon	Common
	Syncope	Uncommon	Uncommon*
	Confusional state	Rare	Very rare
	Hypertonia	Very rare	-
	Peripheral neuropathy	Very rare	-
	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 disturbances	Common	Common
	Diplopia	Common	-
Ear and labyrinth disorders	Tinnitus	Uncommon	Common
	Vertigo	-	Common
Cardiac Disorders	Palpitations	Common	Uncommon*
	Tachycardia	-	Uncommon*
	Angina pectoris (see section 4.4)	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	Very rare	Very rare
	Dysrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Uncommon	Very rare
Vascular Disorders	Flushing	Common	-
	Hypotension (and effects related to hypotension)	Uncommon	Common
	Vasculitis	Very Rare	Uncommon*
	Raynaud's phenomenon		Not known
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Common	Common
	Cough	Uncommon	Common
	Bronchospasm	-	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastro-intestinal Disorders	Gingival hyperplasia	Very rare	-
	Abdominal pain	Common	Common
	Nausea	Common	Common
	Vomiting	Uncommon	Common

	Dyspepsia	Common	Common
	Altered bowel habits	Common	-
	Dry mouth	Uncommon	Uncommon
	Diarrhoea	Common	Common
	Constipation	Common	Common
	Pancreatitis	Very rare	Very rare
	Gastritis	Very rare	-
Hepato-biliary Disorders	Hepatitis, jaundice Hepatitis either cytolitic or cholestatic (see section 4.4)	Very rare -	- Very rare
	Hepatic enzymes increased (mostly consistent with cholestasis)	Very rare	-
Skin and Subcutaneous Tissue Disorders	Quincke's oedema	Very rare	-
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)	Very rare	Uncommon
	Erythema multiforme	Very rare	Very rare
	Alopecia	Uncommon	-
	Purpura	Uncommon	-
	Skin discolouration	Uncommon	-
	Hyperhidrosis	Uncommon	Uncommon
	Pruritus	Uncommon	Common
	Rash, exanthema	Uncommon	Common
	Urticaria (see section 4.4)	Uncommon	Uncommon
	Stevens-Johnson Syndrome	Very rare	-
	Exfoliative dermatitis	Very rare	-

	Toxic Epidermal Necrolysis	Not known	
	Photosensitivity reactions	Very rare	Uncommon*
	Pemphigoid	-	Uncommon*
	Psoriasis aggravation	-	Rare
Musculo-skeletal and Connective Tissue Disorders	Ankle swelling (Joint swelling)	Common	-
	Arthralgia	Uncommon	Uncommon*
	Myalgia	Uncommon	Uncommon*
	Muscle cramps	Common	Common
	Back pain	Uncommon	-
Renal and Urinary Disorders	Micturition disorder, nocturia, increased urinary frequency	Uncommon	-
	Renal impairment	-	Uncommon
	Acute renal failure	-	Very rare
Reproductive System and Breast Disorders	Erectile dysfunction (Impotence)	Uncommon	Uncommon
	Gynaecomastia	Uncommon	-
General Disorders and Administration Site Condition	Oedema	Very Common	-
	Peripheral oedema	-	Uncommon*
	Fatigue	Common	-
	Chest pain	Uncommon	Uncommon*
	Asthenia	Common	Common
	Pain	Uncommon	-
	Malaise	Uncommon	Uncommon*
Investigations	Weight increase, weight decrease	Uncommon	-
	Blood urea	-	Uncommon*
	Increased blood creatinine	-	Uncommon*
	Increased blood bilirubin	-	Rare
	Increase hepatic enzyme	-	Rare

	Decrease in haemoglobin and haematocrit	-	Very rare
Injury, poisoning and procedural complications	Fall	-	Uncommon*

* Frequency calculated from clinical trials for adverse events detected from spontaneous reports

Cases of Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) have been reported with other ACE-inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE-inhibitor therapy including perindopril.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**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 information on overdosage with **Mixanval** in humans.

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 prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

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 over dosage is intravenous infusion of 0,9 % sodium chloride solution. If hypotension occurs, the patient should be placed in the shock position. 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 ACE inhibitors and calcium channel blockers, ATC code C09BB04.

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.

Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.

Renal blood flow increases, while the glomerular filtration rate (GFR) is usually unchanged.

The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours trough effects are about 75 - 100 % of peak effects.

In responding patients, the maximum antihypertensive effect is achieved within a month and persists without the occurrence of tachyphylaxis.

Discontinuation of treatment does not lead to a rebound effect.

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.

5.2 Pharmacokinetic properties

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

Perindopril

After oral administration, the absorption of perindopril is rapid 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 (27 %) 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.

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

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. 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.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure (see section 4.2). 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 section 4.2).

Amlodipine

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.

The terminal plasma elimination half-life is about 35 - 50 hours. 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

Use in the elderly

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC (approximately by 40 – 60 %) and elimination half-life in elderly patients.

Use in patients with impaired hepatic function

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 %.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Cellulose, microcrystalline (E460)

Silica, colloidal anhydrous (E551)

Magnesium stearate (E470B)

Excipient with known effect lactose monohydrate.

Contains sugar (lactose) 65,23 mg for 5/5; 135,47 mg for 5/10 mg; 137,40 mg for 10/5 mg and 130,47 mg for 10/10 mg.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 ºC.

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

Store in the original packaging.

6.5 Nature and contents of container

A white polypropylene container equipped with a low density polyethylene flow reducer and a low density white polyethylene stopper containing desiccant gel, with 30 tablets placed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGIATRATION

Servier Laboratories South Africa (Pty) Ltd

Building Number 4

Country Club Estate

21 Woodlands Drive

Woodmead

2191

8. REGISTRATION NUMBERS

Mixanval 5 mg/5 mg tablets 43/7.1.3/0937

Mixanval 5 mg/10 mg tablets 43/7.1.3/0938

Mixanval 10 mg/5 mg tablets 43/7.1.3/0939

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

5 December 2013

10. DATE OF REVISION OF THE TEXT

17 April 2020