Arplexam 5/1,25/5 mg; 5/1,25/10 mg; 10/2,5/5 mg; 10/2,5/10 mg

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

Arplexam 5/1,25/ 5mg film-coated tablets.

Arplexam 5/1,25/10 mg film-coated tablets.

Arplexam 10/2,5/5 mg film-coated tablets.

Arplexam 10/2,5/10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Arplexam 5/1,25/5 mg: One film-coated tablet contains 3,395 mg perindopril equivalent to 5 mg perindopril arginine, 1,25 mg indapamide and 6,935 mg amlodipine besilate equivalent to 5 mg of amlodipine.

Arplexam 5/1,25/10 mg: One film-coated tablet contains 3,395 mg perindopril equivalent to 5 mg perindopril arginine, 1,25 mg indapamide and 13,870 mg amlodipine besilate equivalent to 10mg of amlodipine.

Arplexam 10/2,5/5 mg: One film-coated tablet contains 6,790 mg perindopril equivalent to 10 mg perindopril arginine, 2,5 mg indapamide and 6,935 mg amlodipine besilate equivalent to 5 mg of amlodipine.

Arplexam 10/2,5/10 mg: One film-coated tablet contains 6,790 mg perindopril equivalent to 10 mg perindopril arginine, 2,5 mg indapamide and 13,870 mg amlodipine besilate equivalent to 10 mg of amlodipine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Arplexam 5/1,25/5 mg: white, oblong, film-coated tablet, 9,75 mm long and 5,16 mm wide, engraved with  on one face and  on the other face.

Arplexam 5/1,25/10 mg: white, oblong, film-coated tablet, 10,7 mm long and 5,66 mm wide, engraved with  on one face and  on the other face.

Arplexam 10/2,5/5 mg: white, oblong, film-coated tablet, 11,5 mm long and 6,09 mm wide, engraved with  on one face and  on the other face.

Arplexam 10/2,5/10 mg: white, oblong, film-coated tablet, 12,2 mm long and 6,46 mm wide, engraved with  on one face and  on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Arplexam is indicated as substitution therapy for treatment of essential hypertension, in adult patients already controlled with amlodipine and the fixed dose combination perindopril/indapamide, taken at the same dose levels as contained in Arplexam.

4.2 Posology and method of administration

Posology

One Arplexam film-coated tablet per day as a single dose, preferably to be taken in the morning and before a meal.

Arplexam is not suitable for initial therapy.

If a change of the posology is required, titration should be done with the individual components.

Special populations

Renal impairment (see sections 4.3 and 4.4)

In severe renal impairment (creatinine clearance below 30 mL/min), treatment is contraindicated.

In patients with moderate renal impairment (creatinine clearance 30 - 60 mL/min), Arplexam at the doses 10/2,5/5 mg and 10/2,5/10 mg is contraindicated. It is recommended to start treatment with appropriate doses of the individual components.

Frequent monitoring of blood pressure, creatinine and potassium should be done.

Concomitant use of perindopril with aliskiren is contraindicated in patients with renal impairment (GFR < 60 ml/min/1,73 m^2) (see section 4.3).

Hepatic impairment (see sections 4.3, 4.4 and 5.2)

Arplexam is contraindicated in patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. Safety of Arplexam has not been established in these patients.

Elderly (see section 4.4)

Elimination of perindoprilat is decreased in the elderly (see section 5.2).

Elderly can be treated with Arplexam according to renal function (see section 4.3).

Paediatric population

The safety and efficacy of Arplexam in children and adolescents below 18 years of age, have not been established. No data are available.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to any of the ingredients of Arplexam.
- 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.
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5)
- Porphyria
- Lithium therapy: Concomitant administration with Arplexam may lead to toxic blood concentrations of lithium (see section 4.5)
- Pregnancy and lactation
- Concomitant use of Arplexam with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60mL/min/1,73m^2) (see sections 4.5 and 5.1)
- Dialysis patients
- Patients with untreated decompensated heart failure
- Moderate renal impairment (creatinine clearance below 60 mL/min) for Arplexam doses containing 10/2,5 mg of perindopril/indapamide combination (i.e., Arplexam 10/2,5/5 mg and 10/2,5/10 mg)
- Hepatic encephalopathy
- Moderate hepatic impairment (Child Pugh B) and severe hepatic impairment (Child Pugh C)
- Hypokalaemia
- 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.
- Concomitant use with sacubitril/valsartan. Arplexam must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5).
- 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.

4.4 Special warnings and precautions for use

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

All warnings related to each component, as listed below, should apply also to the fixed combination of Arplexam

Special warnings

Lithium

Lithium should not be used in combination with perindopril/indapmide as contained in Arplexam (see sections 4.3 and 4.5).

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

The concomitant use of ACE-inhibitors, such as contained in Arplexam angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal

function (including acute renal failure). be used for dual blockade of RAAS (see sections 4.3, 4.5 and 5.1).

ACE-inhibitors such as contained in Arplexam and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Concomitant use of fluoroquinolones

Concomitant use of fluoroquinolones and ACE-inhibitors/Angiotensin such as contained in Arplexam or 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.

Potassium-sparing medicines, potassium supplements or potassium-containing salt substitutes

The combination of perindopril such as contained in Arplexam, and potassium-sparing medicines, potassium supplements or potassium-containing salt substitutes are not recommended (see section 4.5).

Neutropenia/agranulocytosis/thrombocytopenia/anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors such as contained in Arplexam. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril 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

perindopril is used in such patients, periodical monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever) (see section 4.8).

Renovascular hypertension

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

Hypersensitivity/angioedema

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including perindopril as contained in Arplexam. This may occur at any time during treatment. In such cases Arplexam should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been 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, appropriate therapy, which may include subcutaneous epinephrine solution 1:1 000 (0,3 ml to 0,5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE-inhibitors such as contained in Arplexam have been reported to have a higher incidence of angioedema compared to non-blacks.

Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE-inhibitor (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 such as contained in Arplexam presenting with abdominal pain.

Sacubitril/valsartan

The combination of perindopril such as contained in Arplexam, 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 NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin)

Patients taking concomitant NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) 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). 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.

Anaphylactoid reactions during desensitisation

There have been reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE-inhibitors such as contained in Arplexam, during desensitisation treatment with hymenoptera (bees, wasps) venom. ACE-inhibitors should be used with caution in allergic patients treated with desensitisation, and avoided in those undergoing venom immunotherapy. However these reactions could be prevented by temporary withdrawal of the ACE-inhibitor for at least 24 hours before treatment in patients who require both ACE-inhibitors and desensitisation.

Anaphylactoid reactions during LDL apheresis

Patients receiving ACE-inhibitors such as contained in Arplexam, 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.

Haemodialysis patients

Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE-inhibito such as contained in Arplexam. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive medicine.

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 Arplexam is not recommended.

Hepatic encephalopathy

When liver function is impaired, thiazide diuretics and thiazide-related diuretics such as contained in Arplexam may cause particularly in case of electrolyte imbalance, hepatic encephalopathy which can progress to hepatic coma.

Administration of Arplexam should be stopped immediately if this occurs.

Photosensitivity

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

Precautions for use

Renal function

- In cases of severe renal impairment (creatinine clearance < 30 mL/min), treatment is contraindicated.
- For patients with a moderate renal impairment (creatinine clearance < 60 mL/min), treatment is contraindicated with Arplexam doses containing 10/2,5 mg of perindopril /indapamide combination (i.e., Arplexam 10/2,5/5 mg and 10/2,5/10 mg).
- In hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests are indictive of functional renal insufficiency, treatment with Arplexam should be stopped and alternative treatment options to be considered.

  Renal failure has been reported in patients with severe heart failure or underlying renal failure including renal artery stenosis.

  Arplexam should not be used in patients with bilateral renal artery stenosis or a single functioning kidney.

Marked stimulation of the renin-angiotensin-aldosterone system has been observed with perindopril such as contained in Arplexam, with a risk of arterial hypotension and/or renal failure in patients with cardiac insufficiency and/or during marked water and electrolyte depletions (strict sodium restricted diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites.

The blocking of this system with an angiotensin converting enzyme inhibitor such as contained in Arplexam may cause, either at the time of the first administration and/or during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, indicating impending/imminent renal failure.

In such cases, the treatment should be discontinued and other treatment options be considered. In patients with ischaemic heart or cerebrovascular disease an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

- Thiazide diuretics and thiazide-related diuretics such as contained in Arplexam, are only fully effective when renal function is normal or only slightly impaired (creatinine levels lower than approximately 25 mg/l, i.e. 220 µmol/l for an adult).

  In the elderly the value of plasma creatinine levels should be adjusted in relation to age, weight and gender.

  Hypovolaemia, secondary to the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration which may result in an increase in blood urea and creatinine levels with functional renal insufficiency. This may be reversible in patients with normal renal function but may lead to a further deterioration of renal function in patients with pre-existing impairment of renal function.
- Amlodipine such as contained in Arplexam, may be used at approved doses in patients with renal failure. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

- The effect of the combination Arplexam has not been tested in renal dysfunction. In renal impairment, Arplexam doses should respect those of the individual components taken separately.

Hypotension and water and sodium depletion

- There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore clinical examinination and laboratory tests should be used to exclude signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhoea or vomiting. Regular monitoring of plasma urea, creatinine, hydration status and plasma electrolytes should be carried out in such patients.

  Marked hypotension may require the implementation of an intravenous infusion of 0,9 % sodium chloride (isotonic saline).

  Transient hypotension is not a contraindication to continuation of treatment. After re-establishment of a satisfactory blood volume and blood pressure, treatment can be started again at a reduced dose or treatment with Arplexam should be stopped and treatment with mono-component medicines be considered.
- Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential.

  Testing should be more frequent in elderly and cirrhotic patients (see sections 4.8 and 4.9).

  Any diuretic including the diuretic contained in Arplexam may cause hyponatraemia, with serious consequences.

  Hyponatraemia with hypovolaemia may cause dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis.

Potassium levels

- The combination of indapamide with perindopril and amlodipine as contained in Arplexam, does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. Frequent monitoring of plasma potassium levels should be done.
- Elevations in serum potassium have been observed in patients treated with ACE-inhibitors, including perindopril as contained in Arplexam. 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), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicine associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole) and especially aldosterone antagonists or angiotensin-receptor blockers. 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, dysrhythmias which may be fatal. If concomitant use of the above-mentioned medicines is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).
- Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics such as contained in Arplexam. Hypokalaemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of lowered potassium levels (< 3,4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, patients with coronary artery disease and patients with heart failure.

In such cases hypokalaemia increases the cardiac toxicity of digoxin and the risk of rhythm disorders.

Subjects presenting with a long QT interval (congenital or iatrogenic) are also at risk. Hypokalaemia, as with bradycardia, may trigger the onset of severe rhythm disorders, in particular *torsades de pointes*, which may be fatal.

Plasma potassium levels should be measured, during the first week of treatment and frequently monitored thereafter. If low potassium levels are detected, correction is required.

Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

Calcium levels

Thiazide diuretics and thiazide-related diuretics such as contained in Arplexam, may reduce urinary excretion of calcium and cause a transient increase in plasma calcium levels. Markedly raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases the treatment should be stopped before investigating the parathyroid function (see section 4.8).

Plasma magnesium:

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8).

Renovascular hypertension

The treatment for renovascular hypertension is revascularisation. Angiotensin converting enzyme inhibitors such as contained in Arplexam may cause a deterioraton in renal function and alternative treatment options should be considered.

Cough

A dry cough has been reported with the use of angiotensin converting enzyme inhibitors such as contained in Arplexam. It is characterised by its persistence and by its disappearance when treatment is withdrawn.

Atherosclerosis

The risk of hypotension exists in all patients but particular care should be taken in patients with ischaemic heart disease or cerebral circulatory insufficiency, with treatment being started at a low dose.

Hypertensive crisis

The safety and efficacy of Arplexam as treatment for a hypertensive crisis, have not been established.

Cardiac failure/severe cardiac insufficiency

Patients with heart failure NYHA class III and IV should not be treated with Arplexam (see section 4.3).

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 as contained in Arplexam, treated group than in the placebo group. Calcium channel blockers, including amlodipine, should not be used in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Aortic or mitral valve stenosis / hypertrophic cardiomyopathy

ACE-inhibitors such as contained in Arplexam, should not be used in patients with an obstruction in the outflow tract of the left ventricle (see section 4.3).

Diabetic patients

Caution is advised when Arplexam is used for treatment of essential hypertension in patients with insulin dependent diabetes mellitus. Frequent monitoring of blood pressure, blood potassium and blood glucose should be done.

Ethnic differences

Angiotensin converting enzyme inhibitors, including perindopril as contained in Arplexam**,** is 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. They may also have a higher risk to develop angioedema.

Surgery / anaesthesia

Angiotensin converting enzyme inhibitors such as perindopril contained in Arplexam, can cause hypotension during anaesthesia, especially if hypotension is also a known adverse reaction of the anaesthetic administered.

It is recommended that Arplexam should be discontinued where possible one day before surgery.

Hepatic impairment

Safety of Arplexam in patients with any hepatic impairment has not been established.

Arplexam use is contraindicated in patients with moderate impairment of hepatic function (Child Pugh B) and in patients with severe hepatic impairment (Child Pugh C).

ACE-inhibitors such as contained in Arplexam, have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis which may be fatal. The mechanism of this syndrome is not understood. Patients receiving ACE-inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue Arplexam and receive appropriate medical follow-up (see section 4.8).

The half-life of amlodipine as contained in Arplexam, is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established.

Uric acid

Arplexam may increase the risk of gout attacks in hyperuricaemic patients.

Elderly

Renal function and potassium levels should be tested before the start of treatment. The initial dose is subsequently adjusted according to blood pressure response, especially in cases of water and electrolyte depletion, in order to avoid sudden onset of hypotension.

In the elderly increase of the dosage of amlodipine should take place with care (see sections 4.2 and 5.2).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulphonamide or sulphonamide derivative medicines can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue the medicine intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Prohibited medicines for athletes

Arplexam contins the diuretic indapamide, which is a prohibited medicine for athletes.

Atheletes will test positive for a prohibited medicine if they are on treatment with Arplexam.

Excipients

Level of sodium.

Arplexam contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Dual blockade of the RAAS with ARB's, 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 such as contained in Arplexam, 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 agent (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). 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 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: aliskiren, potassium salts, potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), ACE-inhibitors such as contained in Arplexam, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride.. The combination of these medicine increases the risk of hyperkalaemia.

Therefore, the combination of Arplexam 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 with Arplexam is contraindicated (see section 4.3)

Aliskiren

Concomitant use with Arplexam in patients with diabetes mellitus or patients with impaired renal function, increases the risk of hyperkalaemia, further deterioration of renal function and cardiovascular morbidity and mortality.

Fluoroquinolones

Concomitant use of fluoroquinolones and ACE-inhibitors such as contained in Arplexam, 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).

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 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 such as contained in Arplexam, with sacubitril/valsartan is contraindicated as the concomitant inhibition of neprilysin and ACE may increase the risk of angioedema. Sacubitril/valsartan must not be started until 36 hours after taking the last dose of Arplexam must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Lithium

Concomitant use of lithium with ACE-inhibitors such as perindopril contained in Arplexam is contraindicated. Lithium blood concentrations may increase toxic levels with concomitant use of Arplexam.

Concomitant use not recommended

Components of Arplexam	**Known interaction with the following medicine**	**Interaction with other medicines**
perindopril	Concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker	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 medicine. Dual blockade (e.g, by combining an ACE-inhibitor with an angiotensin II receptor antagonist) is not recommended. (see section 4.4)
	Estramustine	Risk of increased adverse effects such as angioneurotic oedema (angioedema).
	Potassium-sparing medicine (e.g triamterene, amiloride,…), potassium (salts),	Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). The combination of perindopril as contained in Arplexam, with the above-mentioned medicine is not recommended (see section 4.4). For use of spironolactone in heart failure, see "Concomitant use which requires special care".
	Co-trimoxazole (trimethoprim/sulfamethoxazole)	Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

amlodipine	Dantrolene (infusion)	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, 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
	Grapefruit or grapefruit juice	The bioavailability may be increased in some patients resulting in increased blood pressure lowering effects

Concomitant use which requires special care

Component of Arplexam	Known interaction with the following medicine	Interaction with other medicines
perindopril/ indapamide /	Baclofen	Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.
	Non-steroidal anti-inflammatory medicinal products (included acetyl salicylic acid at high doses)	When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory medicine (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 ACE-inhibitors 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.
perindopril	Antidiabetic medicines (insulin, oral hypoglycaemic medicines)	Concomitant administration of ACE-inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic medicines) 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 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 therapy with low and progressive doses of perindopril. In arterial hypertension, when prior diuretic therapy can have and/or caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE-inhibitor, in which case a

Component of Arplexam	**Known interaction with the following medicine**	**Interaction with other medicines**
		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. Frequent monitoring of 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).

Component of Arplexam	**Known interaction with the following medicine**	**Interaction with other medicines**
indapamide	*Torsades de pointes* inducing medicine	Due to the risk of hypokalemia, indapamide should be administered with caution when associated with medicines that induced *torsades de pointes* such as: - class IA anti-dysrhythmic medicines (quinidine, hydroquinidine, disopyramide); - class III anti-dysrhythmic medicines (amiodarone, dofetilide, ibutilide, bretylium, sotalol); - some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, sultopride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); - other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of low potassium levels and correction if necessary monitoring of the QT interval.
	Amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives	Increased risk of low potassium levels (additive effect). Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with digoxin. Non stimulant laxatives should be used.
	Digoxin	Hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digoxin. Potassium levels, magnesium and ECG should be monitored and treatment reconsidered if necessary.
	Allopurinol	Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Component of Arplexam	**Known interaction with the following medicine**	**Interaction with other medicines**
amlodipine	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

Component of Arplexam	**Known interaction with the following medicines**	**Interaction with other medicines**
perindopril/ indapamide /amlodipine	Imipramine-like antidepressants (tricyclics), neuroleptics	Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).
	other antihypertensive medicines	Use of other antihypertensive medicines could result in additional blood pressure lowering effect.
	Corticosteroids, tetracosactide	Reduction in antihypertensive effect (salt and water retention due to corticosteroids).
perindopril	Antihypertensive medicines and Vasodilators	Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure
	Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide	Concomitant administration with ACE-inhibitors may lead to an increased risk for leukopenia.
	Anaesthetic medicine	ACE-inhibitors may enhance the hypotensive effects of certain anaesthetic medicines
	Diuretics (thiazide or loop diuretics)	Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypotension when initiating therapy with perindopril.
	Gliptins (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.
	Sympathomimetics	Sympathomimetics may reduce the antihypertensive effects of ACE-inhibitors
	Gold	Nitritoid reactions (symptoms include facial flushing,

Component of Arplexam	**Known interaction with the following medicines**	**Interaction with other medicines**
		nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE-inhibitor therapy including perindopril.
indapamide	Metformin	Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics. Do not use metformin when plasma creatinine levels exceed (15 mg/l) 135 micromol/l in men and (12 mg/l) 110 micromol/l in women.
	Iodinated contrast media	In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.
	Calcium (salts)	Risk of increased levels of calcium due to reduced elimination of calcium in the urine.
	Ciclosporin	Risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no salt and water depletion.
amlodipine	Atorvastatin, digoxin or warfarin	In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.
	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

Component of Arplexam	Known interaction with the following medicines	Interaction with other medicines
		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 to 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.

4.6 Fertility, pregnancy and lactation

Arplexam is contraindicated during pregnancy and lactation.

Pregnancy

Perindopril

The use of Arplexam is contraindicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take Arplexam 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 Arplexam 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.

Arplexam passes through the placenta and causes disturbance in foetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of ACE-inhibitors, such as Arplexam, 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).

Indapamide

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of indapamide in pregnant women. Prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a feto-placental ischemia and growth retardation. Moreover, cases of hypoglycemia and thrombocytopenia in neonates have been reported following exposure near term.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Amlodipine

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Breastfeeding

Arplexam is contraindicated during lactation.

Perindopril

Because no information is available regarding the use of perindopril during breastfeeding, perindopril is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Indapamide

There is insufficient information on the excretion of indapamide/metabolites in human milk. Hypersensitivity to sulphonamide-derived medicines and hypokalaemia might occur. A risk to newborns/infants cannot be excluded.

Indapamide is closely related to thiazide diuretics which have been associated, during breastfeeding, with a decrease or even suppression of milk lactation.

Amlodipine

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

Common to perindopril and indapamide

Reproductive toxicity studies showed no effect on fertility in female and male rats (see section 5.3). No effects on human fertility are anticipated.

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

No studies on the effects of Arplexam on the ability to drive and use machines have been performed. Arplexam may affect the ability to drive and use machines. Patients should not drive and use machines until they know how the treatment with Arplexam affects them.

Perindopril and indapamide may cause hypotension which may affect the ability of patients to drive and use machines.

Amlodipine can cause hypotension, dizziness, headache, visual impairment, fatigue, weariness or nausea, which may impair the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile.

The most commonly reported adverse reactions with perindopril, indapamide and amlodipine given separately are: hypokalaemia, dizziness, headache, paraesthesia, somnolence, dysgeusia, visual impairment, diplopia, tinnitus, vertigo, palpitations, flushing, hypotension (and effects related to hypotension), cough, dyspnoea, gastro-intestinal disorders (abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting, change of bowel habit), pruritus, rash, rash maculo-papular, muscle spasms, ankle swelling, asthenia, oedema and fatigue.

Tabulated list of adverse reactions

The following undesirable effects have been observed with perindopril, indapamide or amlodipine during treatment and ranked 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		
		Perindopril	**Indapamide**	**Amlodipine**
Infections and infestations	Rhinitis	Very rare	-	Uncommon
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Rare	-	-
Blood and Lymphatic System Disorders	Eosinophilia	Uncommon*	-	-
	Agranulocytosis (see section 4.4)	Very rare	Very rare	-
	Pancytopenia	Very rare	-	-
	Aplastic anaemia	-		Very rare
	Leukopenia (see section 4.4)	Very rare	Very rare	Very rare
	Neutropenia (see section 4.4)	Very rare	-	-
	Haemolytic anaemia	Very rare	Very rare	-
	Thrombocytopenia (see section 4.4)	Very rare	Very rare	Very rare
Immune System Disorders	Hypersensitivity	-	Uncommon	Very rare

Metabolism and Nutrition Disorders	Hypoglycaemia (see sections 4.4 and 4.5)	Uncommon*	-	-
	Hyperkalaemia reversible on discontinuation (see section 4.4)	Uncommon*	-	-
	Hypokalaemia, (see section 4.4)	-	Common	-
	Hyponatraemia (see section 4.4)	Uncommon*	Uncommon	
	Hypochloraemia	-	Rare	-
	Hypomagnesaemia	-	Rare	-
	Hyperglycaemia	-	-	Very rare
	Hypercalcaemia	-	Very rare	-
Psychiatric disorders	Insomnia	-	-	Uncommon
	Mood altered (including anxiety)	Uncommon	-	Uncommon
	Depression	Uncommon*	-	Uncommon
	Sleep disorder	Uncommon	-	-
	Confusional state	Very rare	-	Rare
Nervous System disorders	Dizziness	Common	-	Common
	Headache	Common	Rare	Common
	Paraesthesia	Common	Rare	Uncommon
	Somnolence	Uncommon*	-	Common

	Hypoaesthesia	-	-	Uncommon
	Dysgeusia	Common	-	Uncommon
	Tremor	-	-	Uncommon
	Syncope	Uncommon*	Not known	Uncommon
	Hypertonia	-	-	Very rare
	Neuropathy peripheral	-	-	Very rare
	Extrapyramidal disorder (extrapyramidal syndrome)	-	-	Not known
	Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	Very rare	-	-
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4)	-	Not known	-
Eye Disorders	Visual impairment	Common	Not known	Common
	Acute angle-closure glaucoma	-	Not known	-
	Choroidal effusion	-	Not known	-
	Diplopia	-	-	Common
	Myopia	-	Not known	-
	Vision blurred	-	Not known	-

Ear and labyrinth disorders	Tinnitus	Common	-	Uncommon
	Vertigo	Common	Rare	-
Cardiac Disorders	Palpitations	Uncommon*	-	Common
	Tachycardia	Uncommon*	-	-
	Angina pectoris (see section 4.4)	Very rare	-	-
	Dysrthymia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Very rare	Very rare	Uncommon
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	Very rare	-	Very rare
	Torsade de pointes (potentially fatal) (see sections 4.4 and 4.5)	-	Not known	-
Vascular Disorders	Flushing	Rare*	-	Common
	Hypotension (and effects related to	Common	Very rare	Uncommon

	hypotension) (see section 4.4)			
	Vasculitis	Uncommon*	-	Very rare
	Raynaud's phenomenon	Not known	-	-
Respiratory, Thoracic and Mediastinal Disorders	Cough (see section 4.4)	Common	-	Uncommon
	Dyspnoea	Common	-	Common
	Bronchospasm	Uncommon	-	-
	Eosinophilic pneumonia	Very rare	-	-
Gastro-intestinal Disorders	Abdominal pain	Common	-	Common
	Constipation	Common	Rare	Common
	Diarrhoea	Common	-	Common
	Dyspepsia	Common	-	Common
	Nausea	Common	Rare	Common
	Vomiting	Common	Uncommon	Uncommon
	Dry mouth	Uncommon	Rare	Uncommon
	Change of bowel habit	-	-	Common
	Gingival hyperplasia	-	-	Very rare
	Pancreatitis	Very rare	Very rare	Very rare
	Gastritis	-	-	Very rare
Hepato-biliary Disorders	Hepatitis (see section 4.4)	Very rare	Not known	Very rare

	Jaundice	-	-	Very rare
	Hepatic function abnormal	-	Very rare	-
Skin and Subcutaneous Tissue Disorders	Pruritus	Common	-	Uncommon
	Rash	Common	-	Uncommon
	Maculo-papular rash		Common	-
	Urticaria (see section 4.4)	Uncommon	Very rare	Uncommon
	Angioedema (see section 4.4)	Uncommon	Very rare	Very rare
	Alopecia	-	-	Uncommon
	Purpura	-	Uncommon	Uncommon
	Skin discolouration	-	-	Uncommon
	Hyperhidrosis	Uncommon	-	Uncommon
	Exanthema	-	-	Uncommon
	Photosensitivity reaction	Uncommon*	Not known (see section 4.4)	Very rare
	Psoriasis aggravation	Rare	-	-
	Pemphigoid	Uncommon*	-	-
	Erythema multiforme	Very rare	-	Very rare
	Stevens-Johnson Syndrome	-	Very rare	Very rare
	Exfoliative dermatitis	-	-	Very rare

	Toxic epidermal necrolysis	-	Very rare	Not known
	Quincke's oedema (angioedema)	-	-	Very rare
Musculoskeletal And Connective Tissue Disorders	Muscle spasms	Common	Not known	Common
	Ankle swelling	-	-	Common
	Arthralgia	Uncommon**	-	Uncommon
	Muscular weakness	-	Not known	-
	Myalgia	Uncommon*	Not known	Uncommon
	Rhabdomyolysis	-	Not known	-
	Back pain	-	-	Uncommon
	Possible worsening of pre-existing systemic lupus erythematosus	-	Not known	-
Renal and Urinary Disorders	Micturition disorder	-	-	Uncommon
	Nocturia	-	-	Uncommon
	Pollakiuria	-	-	Uncommon
	Anuria/Oliguria	Rare*		
	Acute renal failure	Rare	-	-
	Renal failure	Uncommon	Very rare	-

Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon	Uncommon	Uncommon
	Gynaecomastia	-	-	Uncommon
General Disorders and Administration Site Conditions	Asthenia	Common	-	Common
	Fatigue	-	Rare	Common
	Oedema	-	-	Very common
	Chest pain	Uncommon*	-	Uncommon
	Pain	-	-	Uncommon
	Malaise	Uncommon*	-	Uncommon
	Peripheral oedema	Uncommon*	-	-
	Pyrexia	Uncommon*	-	-
Investigations	Weight increased	-	-	Uncommon
	Weight decreased	-	-	Uncommon
	Blood urea increased	Uncommon*	-	-
	Blood creatinine increased	Uncommon*	-	-
	Blood bilirubin increased	Rare	-	-
	Hepatic enzyme increased	Rare	Not known	Very rare

	Haemoglobin decreased and haematocrit decreased (see section 4.4)	Very rare	-	-
	Electrocardiogram QT prolonged (see sections 4.4 and 4.5)	-	Not known	-
	Increased blood glucose	-	Not known	-
	Increased blood uric acid	-	Not known	-
Injury, poisoning and procedural complications	Fall	Uncommon*	-	-

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

Description of selected adverse reactions:

During phase II and III studies comparing indapamide 1,5mg and 2,5mg, plasma potassium analysis showed a dose-dependent effect of indapamide:

- Indapamide 1.5mg: Plasma potassium < 3,4 mmol/l was seen in 10 % of patients and < 3,2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0,23 mmol/l.

- Indapamide 2.5 mg: Plasma potassium <3.4 mmol/l was seen in 25 % of patients and < 3.2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. 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 Arplexam in humans.

For perindopril/indapamide combination

Symptoms

The most likely adverse reaction in cases of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria which may progress to anuria (due to hypovolaemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.

Management

The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, and restoring the fluid and electrolyte balance.
If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an intravenous infusion of 0,9 % sodium chloride (isotonic saline) may be given, or any other method of volaemic expansion may be used.
Perindoprilat, the active form of perindopril, can be dialysed (see section 5.2).

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.

Management

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE-inhibitors, combinations. ACE-inhibitors, calcium channel blockers and diuretics. ATC code: C09BX01.

Arplexam is a combination of three antihypertensive components with complementary mechanisms to control blood pressure in patient with hypertension. Perindopril arginine salt is an

angiotensin converting enzyme inhibitor, indapamide, a chlorosulphamoyl diuretic and amlodipine, a calcium ion flux inhibitor of the dihydropyridine group.

The pharmacological properties of Arplexam are derived from those of each of the components taken separately. In addition, the combination of perindopril/indapamide produces an additive synergy of the antihypertensive effects of the two components.

Mechanism of action

Perindopril

Perindopril is an inhibitor of the angiotensin converting enzyme (ACE-inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; in addition the enzyme stimulates the secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides.

This results in:

- a reduction in aldosterone secretion,
- an increase in plasma renin activity, since aldosterone no longer exercises negative feedback,
- a reduction in total peripheral resistance with a preferential action on the vascular bed in muscle and the kidney, with no accompanying salt and water retention or reflex tachycardia, with chronic treatment.

The antihypertensive action of perindopril occurs in patients with low or normal renin concentrations.

Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive.

Perindopril reduces the work of the heart:

- by a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins : reduction in pre-load,
- by reduction of the total peripheral resistance: reduction in afterload.

Studies carried out on patients with cardiac insufficiency have shown:

- a reduction in left and right ventricular filling pressures,

- a reduction in total peripheral vascular resistance,
- an increase in cardiac output and an improvement in the cardiac index,
- an increase in regional blood flow in muscle.

Exercise test results also showed improvement.

Indapamide

Indapamide is a sulfonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

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.

Pharmacodynamic effects

Perindopril/indapamide

In hypertensive patients regardless of age, the perindopril/indapamide combination exerts a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the medicines administered alone.

Perindopril

Perindopril is active in all grades of hypertension: mild to moderate or severe. A reduction in systolic and diastolic arterial pressure is observed in the lying and standing position.

The antihypertensive activity after a single dose is maximal at between 4 and 6 hours and is maintained over 24 hours.

There is a high degree of residual blocking of angiotensin converting enzyme at 24 hours, approximately 80 %.

In patients who respond, normalised blood pressure is reached after one month and is maintained without tachyphylaxis.

Withdrawal of treatment has no rebound effect on hypertension.

Perindopril has vasodilatory properties and restores elasticity of the main arterial trunks, corrects histomorphometric changes in resistance arteries and produces a reduction in left ventricular hypertrophy.

If necessary, the addition of a thiazide diuretic leads to an additive synergy.

The combination of an angiotensin converting enzyme inhibitor with a thiazide diuretic decreases the hypokalaemia risk associated with the diuretic alone.

Indapamide

Indapamide, as monotherapy, has an antihypertensive effect which lasts for 24 hours. This effect occurs at doses at which the diuretic properties are minimal.

Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance.

Indapamide reduces left ventricular hypertrophy.

When a dose of thiazide diuretic and thiazide-related diuretics such as indapamide is exceeded, the antihypertensive effect reaches a plateau, whereas the adverse effects continue to increase. If the treatment is ineffective, the dose should not be increased.

Furthermore, it has been shown that in the short-term, mid-term and long-term in hypertensive patients, indapamide:

- has no effect on lipid metabolism: triglycerides, LDL-cholesterol and HDL-cholesterol,
- has no effect on carbohydrate metabolism, even in diabetic hypertensive patients.

Amlodipine

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

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. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Clinical efficacy and safety

Arplexam has not been studied on morbidity and mortality.

Perindopril/indapamide

PICXEL, a multicenter, randomised, double blind active controlled study has assessed on echocardiography the effect of perindopril/indapamide combination on LVH versus enalapril monotherapy.

In PICXEL, hypertensive patients with LVH (defined as left ventricular mass index (LVMI) > 120 g/m^2 in male and > 100 g/m^2 in female) were randomised either to perindopril tert-butylamine 2 mg (equivalent to 2,5 mg perindopril arginine)/ indapamide 0,625 mg or to enalapril 10 mg once a day for a one-year treatment. The dose was adapted according to blood pressure control, up to perindopril tert-butylamine 8 mg (equivalent to 10 mg perindopril arginine) and indapamide 2,5 mg or enalapril 40 mg once a day. Only 34 % of the subjects remained treated with perindopril tert-butylamine 2 mg (equivalent to 2,5 mg perindopril arginine)/ indapamide 0,625mg (versus 20 % with enalapril 10 mg).

At the end of treatment, LVMI had decreased significantly more in the perindopril/indapamide group (- 10,1 g/m²) than in the enalapril group (- 1,1 g/m²) in the all randomised patients population. The between group difference in LVMI change was - 8,3 (95 % CI (- 11,5, - 5,0), p < 0,0001).

A better effect on LVMI was reached with higher perindopril/indapamide doses than those licensed for perindopril/indapamide 2,5 mg/0,625 mg and perindopril/indapamide 5 mg/1,25 mg.

Regarding blood pressure, the estimated mean between-group differences in the randomised population were - 5,8 mmHg (95 % CI (- 7,9, - 3,7), p < 0,0001) for systolic blood pressure and - 2,3 mmHg (95 % CI (- 3,6, - 0,9), p = 0,0004) for diastolic blood pressure respectively, in favour of the perindopril/indapamide group.

The ADVANCE study was a multicentre, international, randomised, 2 x 2 factorial designed trial aimed at determining the benefits of Blood Pressure lowering with the fixed combination perindopril / indapamide vs placebo on top of current standard therapy (double blind comparison) and of gliclazide MR based intensive glucose control strategy (HbA1c target of 6,5 % or lower) vs

standard glucose control (PROBE [Prospective Randomised Open study with Blinded Evaluation] design) on major macrovascular and microvascular events in type 2 diabetic patients.

The primary end-point was a composite of major macrovascular (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) and microvascular (new or worsening nephropathy and eye disease) events.

Overall, 11 140 type 2 diabetic patients (mean values: age 66 years, BMI 28 kg/m^2, duration of diabetes 8 years, HbA1c 7,5 % and SBP/DBP 145/81 mmHg) were involved in the trial. Among them, 83 % were hypertensive, 32 % and 10 % presented a history of macro- or micro- vascular disease respectively and 27 % had microalbuminuria. Concomitant therapies included BP lowering agents (75 %), lipid lowering agents (35 % mainly statins 28 %), aspirin or other antiplatelets (47 %).

Following a 6-week run-in period on open perindopril / indapamide combination and usual glucose lowering treatment, patients were randomly assigned to placebo (n = 5 571) or perindopril / indapamide combination (n = 5 569).

After a mean duration of follow-up of 4,3 years, the treatment with perindopril / indapamide resulted in a significant relative risk reduction of 9 % in the primary endpoint (95 % CI [0,828; 0,996], p = 0,041).

This benefit was driven by a significant relative risk reduction of 14 % in total mortality (95 % CI [0,75; 0,98], p = 0,025), of 18 % in cardiovascular deaths (95 % CI [0,68 ; 0,98], p = 0,027) and of 21 % in total renal events (95 % CI [0,74; 0,86], p < 0,001) in the perindopril / indapamide group compared to the placebo group.

In the sub-group of interest of hypertensive patients, there was a relative risk reduction of 9 % in the combined major macrovascular and microvascular events in the perindopril / indapamide group compared to the placebo group (95 % CI [0,82; 1,00], p = 0,052).

There were also a significant relative risk reduction of 16 % in total mortality (95 % CI [0,73; 0,97], p = 0,019), of 20 % in cardiovascular deaths (95 % CI [0,66; 0,97], p = 0,023) and of 20 % in

total renal events (95 % CI [0,73; 0,87], p < 0,001) in the perindopril / indapamide group compared to the placebo group.

The benefits of the BP lowering intervention were independent of those observed with the intensive glucose control strategy.

Amlodipine

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2,5 - 10 mg/d (calcium channel blocker) or lisinopril 10 - 40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12,5 - 25 mg/d in mild to moderate hypertension.

A total of 33 357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4,9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51,5 %), type 2 diabetes (36,1 %), HDL-C < 35 mg/dL (11,6 %), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20,9 %), current cigarette smoking (21,9 %).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0,98 (95 % CI (0,90 - 1,07) p = 0,65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10,2 % vs. 7,7%, RR 1,38, (95% CI [1,25 – 1,52] p < 0,001)). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0,96 (95 % CI [0,89 - 1,02] p = 0,20).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) clinical trial data:

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes) have examined the use of combination of an ACE-inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed.

Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population

No data are available with Arplexam in children and adolescents below the age of 18 years.

5.2 Pharmacokinetic properties

Arplexam

The co-administration of perindopril/indapamide and amlodipine does not change their pharmacokinetic properties by comparison to separate administration.

Perindopril

Absorption and bioavailability

After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour (perindopril is a prodrug and perindoprilat the active metabolite). The plasma half-life of perindopril is equal to 1 hour. 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.

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.

Biotransformation

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.

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.

Linearity/non-linearity

There is a linear relationship between the dose of perindopril and its plasma exposure.

Special Populations

- Elderly: Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure.
- Renal impairment: Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).
- In case of dialysis: clearance of perindoprilat is equal to 70 mL/min.
- In patients with cirrhosis: Perindopril pharmacokinetics is modified, 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).

Indapamide

Absorption

Indapamide is rapidly and completely absorbed from the digestive tract.

The peak plasma level is reached in humans approximately one hour after oral administration of the product.

Distribution

Plasma protein binding is 79 %.

Metabolism and Elimination

The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation.

Elimination is mainly in the urine (70 % of the dose) and faeces (22 %) in the form of inactive metabolites.

Special populations

The pharmacokinetics is unchanged in patients with renal insufficiency.

Amlodipine

Absorption and Bioavailability

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 bioavailability of amlodipine is not affected by food intake.

Distribution

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.

Metabolism

Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60 % of metabolites excreted in the urine.

Elimination

The terminal plasma elimination half-life is about 35 - 50 hours and is consistent with once daily dosing.

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 and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

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 %.

5.3 Preclinical safety data

Perindopril

In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

No mutagenicity has been observed in in vitro or in vivo studies.

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed. Fertility was not impaired either in male or in female rats.

No carcinogenicity has been observed in long term studies in rats and mice.

Indapamide

The highest doses administered orally to different animal species (40 to 8 000 times the therapeutic dose) have shown an exacerbation of the diuretic properties of indapamide. The major symptoms of poisoning during acute toxicity studies with indapamide administered intravenously or intraperitoneally were related to the pharmacological action of indapamide, i.e. bradypnoea and peripheral vasodilation.

Indapamide has been tested negative concerning mutagenic and carcinogenic properties.

Reproductive toxicity studies have not shown any embryotoxic or teratogenic effect in rat, mice and rabbit.

Fertility was not impaired either in male or female rats.

Perindopril/indapamide

The perindopril/indapamide combination has slightly increased toxicity than that of its components. Renal manifestations do not seem to be potentiated in the rat. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seem to be increased in the rat (compared to perindopril).

These adverse effects appear at dose levels corresponding to a very marked safety margin by comparison to the therapeutic doses used.

Preclinical studies performed separately with perindopril and indapamide did not show genotoxic, carcinogenic or teratogenic potential.

Amlodipine

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended

human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0,5, 1,25, and 2,5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Calcium carbonate starch compound: Calcium carbonate 90 %, Pregelatinised maize starch 10 %,

Cellulose microcrystalline (E460),

Croscarmellose sodium (E468),

Magnesium stearate (E572),

Colloidal anhydrous silica,

Pregelatinised starch.

Film-coating

Glycerol (E422),

Hypromellose 6mPa.s (E464),

Macrogol 6 000,

Magnesium stearate (E572),

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C.

Keep out of reach of children.

Keep the bottle well closed to protect the tablets from moisture.

6.5 Nature and contents of container

Tablet container of 30 film-coated tablets white polypropylene tablet container and a white opaque stopper containing a desiccant gel placed into a carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Servier Laboratories SA (Pty) Ltd

3rd Flor, Building J

Hertford office Park

90 Bekker Road

Vorna Valley

Midrand

1686

8. REGISTRATION NUMBER(S)

Arplexam 5/1,25/5 mg: 49/7.1.3/1235

Arplexam 5/1,25/10 mg: 49/7.1.3/1236

Arplexam 10/2,5/5 mg: 49/7.1.3/1237

Arplexam 10/2,5/10 mg: 49/7.1.3/1238

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 November 2020

10. DATE OF REVISION OF THE TEXT

12 April 2024