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SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

AMLESSA 4/5 uncoated tablets

AMLESSA 4/10 uncoated tablets

AMLESSA 8/5 uncoated tablets

AMLESSA 8/10 uncoated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMLESSA 4/5, each uncoated tablet contains 4 mg of perindopril erbumine and 5 mg of amlodipine (as besilate).

AMLESSA 4/10, each uncoated tablet contains 4 mg of perindopril erbumine and 10 mg of amlodipine (as besilate).

AMLESSA 8/5, each uncoated tablet contains 8 mg of perindopril erbumine and 5 mg of amlodipine (as besilate).

AMLESSA 8/10, each uncoated tablet contains 8 mg of perindopril erbumine and 10 mg of amlodipine (as besilate).

Sugar free.

For full list of excipients, see section 6.1.

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3. PHARMACEUTICAL FORM

Uncoated tablets

AMLESSA 4/5: white to almost white, round, slightly biconvex tablets with bevelled edges engraved with mark U 1 on one side of the tablet, tablet weight – 140 mg.

AMLESSA 4/10: white to almost white, capsule shaped, biconvex one-side scored tablets engraved with mark U on one side and mark 2 on the other side of the breaker score, tablet weight – 280 mg.

AMLESSA 8/5: white to almost white, round, biconvex tablets with bevelled edges engraved with mark U 3 on one side of the tablet, tablet weight – 280 mg.

AMLESSA 8/10: white to almost white, round, biconvex, one-side scored tablets with bevelled edges. Tablet is engraved with mark U on one side and mark 4 on the other side of the breaker score, tablet weight - 280 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMLESSA is indicated for the treatment of hypertension in patients already stabilised with perindopril and amlodipine at equivalent doses. Treatment of hypertension in patients uncontrolled on either perindopril or amlodipine monotherapy.

4.2 Posology and method of administration

Posology

For oral administration.

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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 **AMLESSA** should be modified.

Special Populations:

Patients with renal impairment and elderly patients (see sections 4.4 and 5.2)

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. **AMLESSA** can be administered in patients with Cl_{cr} ≥ 60 ml/min, and is not suitable for patients with Cl_{cr} < 60 ml/min. In these patients, individual dose titration with the mono components is recommended. **AMLESSA** is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.3). Normal dosage regimens are recommended in the elderly.
Changes in amlodipine plasm 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. In these patients, dose selection should be cautious and should start at the lower end of the dosing range (*see section 4.4* and *section 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

AMLESSA 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 perindopril or any excipients of **AMLESSA**.
- History of angioedema associated with previous ACE inhibitor therapy 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 impairment (creatinine clearance < 30 ml/min) see sections 4.2 and 4.4.
- Bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4).
- Aortic stenosis (see section 4.4),
- Concomitant therapy with potassium sparing diuretics such as spironolactone, amiloride, triamterene (see section 4.5),
- Porphyria,

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- Concomitant use of **AMLESSA** with lithium may lead to toxic blood concentrations of lithium (see section 4.5),
- Concomitant use of **AMLESSA** with aliskiren-containing products is contraindicated (see sections 4.5 and 5.1),
- Pregnancy and lactation (see sections 4.4 and 4.6),
- 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).

Linked to amlodipine:

- Hypersensitivity to amlodipine or to dihydropyridines derivatives,
- Severe hypotension,
- Obstruction of the outflow-tract of the left ventricle (e.g. high-grade aortic stenosis),
- Shock, including cardiogenic shock,
- Hemodynamically unstable heart failure after acute myocardial infarction.

Linked to AMLESSA

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

4.4 Special warnings and precautions for use

Related to AMLESSA

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

Linked to perindopril

Should a woman become pregnant while receiving **AMLESSA**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 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 or aliskiren-containing medicines increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren-containing medicines is therefore contraindicated (see sections 4.5 and 5.1).

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, **AMLESSA** 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 patients' 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 an ACE inhibitor (see section 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors such as **AMLESSA**. 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 excluded in the differential diagnosis of patients on **AMLESSA** presenting with abdominal pain (see section 4.8).

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).

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis

Patients receiving perindopril, as in **AMLESSA,** during low-density lipoprotein (LDL) apheresis with dextran sulfate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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***Anaphylactoid reactions during desensitisation**:*

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitor*s* 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 occurs rarely. **AMLESSA** 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, 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).

Hypotension:

ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely 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 **AMLESSA**. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9 %) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy:

AMLESSA should be given with caution to patients with mitral valve stenosis. **AMLESSA** 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). **AMLESSA** is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min). Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8). **AMLESSA** is contraindicated in some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney due to an increased risk of renal insufficiency. In patients treated with **AMLESSA** 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 **AMLESSA** who develop jaundice or marked elevations of hepatic enzymes should discontinue the **AMLESSA** 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. **AMLESSA** 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. **AMLESSA** induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia:

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In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, **AMLESSA** 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 some patients treated with **AMLESSA.** Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, inter-current 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 medicines associated with increases in serum potassium (e.g. heparin). 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 section 4.3 and 4.5).

Diabetic patients:

In diabetic patients treated with oral antidiabetic medicines 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:

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

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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 (see section 5.1). 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.

Hepatic impairment:

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 **AMLESSA** (fixed dose combination).

Elderly:

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

Renal failure:

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

Interactions:

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The concomitant use of **AMLESSA** with lithium, potassium-sparing drugs or potassium supplements, or dantrolene is contraindicated (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Linked to perindopril

Dual blockage 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-containing medicines is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see sections 4.3 and 4.4).

Concomitant use not recommended:

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:

Although serum potassium remains within the normal limits, hyperkalaemia may occur in some patients using **AMLESSA**. ACE-Inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, triamterene or amiloride, potassium supplements or potassium containing salt substitutes may lead to significant increases in serum potassium and are therefore, not recommended (see section 4.3 and 4.4). If the concomitant use is indicated because of documented hypokalaemia, it should be used cautiously and with frequent monitoring of potassium.

Lithium

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

Estramustine

Risk of increased adverse effects such as angioedema.

Non-steroidal anti-inflammatory medicinal products (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 **AMLESSA** 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 medicines (insulins, oral hypoglycaemic sulphonamides):

The use of ACE-inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides.

Non-potassium-sparing diuretics:

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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 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.

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

Patient taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.3 and 4.4).

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.

Concomitant use to be taken into consideration:

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

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

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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 **AMLESSA**. 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 **AMLESSA**.

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Gold:

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

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

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Combined use which requires special care:

CYP3A4 inducers

There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, St John's Wort (*hypericum perforatum*)) may give a lower plasma concentration of amlodipine. **AMLESSA** should be used with caution together with CYP3A4 inducers.

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 significantly increase the plasma concentration of amlodipine. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

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.

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 increases of trough concentrations of ciclosporin were observed. Consideration should be given to

monitoring ciclosporin levels in patients who have undergone renal transplantation and are treated with 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.

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.

Other concomitant use:

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin. Administration of **AMLESSA** with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Related to AMLESSA:

All of the above and in addition:

Concomitant use which requires special care:

Baclofen:

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

Concomitant use to be taken into consideration:

Antihypertensive medicines (such as beta-blockers) and vasodilators:

Concomitant use of these ***medicines*** may increase the hypotensive effects of **AMLESSA**.

Concomitant use with nitroglycerin and 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 increased risk of orthostatic hypotension.

Amifostine:

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

Tricyclic antidepressants/antipsychotics/anaesthetics:

Increased antihypertensive effect and increased risk of orthostatic hypotension.

4.6 Fertility, pregnancy, and lactation

The use of **AMLESSA** is contra-indicated during pregnancy. Pregnant women should be informed of the potential hazards to the foetus and must not take **AMLESSA** 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 **AMLESSA** should be stopped immediately, and, if appropriate, alternative treatment 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/ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spina bifida) and of kidney malformations.

AMLESSA 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 **AMLESSA** 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)

Related to amlodipine component

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

Related to Perindopril component

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

Related to Amlodipine component

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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. **AMLESSA** is contraindicated in women breastfeeding their babies see section 4.3.

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.

4.7 Effects on ability to drive and use machines

No studies on the effects of **AMLESSA o**n the ability to drive and use machines have been performed. Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

a) Summary of the safety profile

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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, pruritus, rash, exanthema, joint swelling (ankle swelling), muscle spasms, fatigue, asthenia.

b) Tabulated summary of adverse reactions

Adverse effects that have been observed during treatment with amlodipine or perindopril given separately and ranked under the MedDRA classification by body system: Frequent, Less, and not known (cannot be estimated from the available data).

Table 1. Reported with amlodipine/perindopril treatment regimen (*see section 5.1*):

MedDRA System organ class Adverse Effects	**Frequency**	
	Perindopril	**Amlodipine**
Infections and infestations		
Rhinitis	Less frequent	Frequent
Blood and lymphatic system disorders		
Eosinophilia	Frequent	-
Leukopenia/neutropenia (*see section 4.4*)	Less frequent	Less frequent
Agranulocytosis or Pancytopenia (*see section 4.4*)	Less frequent	-
Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (*see section 4.4*)	Less frequent	-

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Thrombocytopenia (*see section 4.4*)	Less frequent	Less frequent
Immune system disorders		
Hypersensitivity	Frequent	Less frequent
Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (*see section 4.4*)	Frequent	Less frequent
Metabolism and nutrition disorders		
Hypoglycaemia (*see section 4.4* and *section 4.5*).	Frequent	-
Hyperkalaemia, reversible on discontinuation (*see section 4.4*)	Frequent	-
Hyponatraemia (*see section 4.4*)	Frequent	-
Hyperglycaemia	-	Less frequent
Psychiatric disorders		
Sleep disturbances	Frequent	-
Insomnia	-	Frequent
Mood changes (including anxiety)	Frequent	Frequent
Depression	-	Frequent
Nervous system disorders		
Somnolence (especially at the beginning of treatment)	-	Frequent
Dizziness (especially at the beginning of treatment)	Frequent	Frequent
Headache (especially at the beginning of treatment)	Frequent	Frequent
Dysgeusia	Frequent	Frequent
Tremor	-	Frequent
Hypoaesthesia	-	Frequent
Paresthaesia	Frequent	Frequent
Drowsiness	Frequent	-

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Syncope	Frequent	Frequent
Confusional state	Less frequent	Less frequent
Hypertonia	-	Less frequent
Neuropathy peripheral	-	Less frequent
Cerebrovascular accident possibly secondary to excessive hypotension in high-risk patients (*see section 4.4*)	Less frequent	-
Extrapyramidal disorder (extrapyramidal syndrome)	-	Not known
Eye disorders		
Visual impairment	Frequent	Frequent
Diplopia	-	Frequent
Ear and labyrinth disorders		
Tinnitus	Frequent	Frequent
Vertigo	-	Frequent
Cardiac disorders		
Palpitations	Frequent	Frequent
Tachycardia	Frequent	-
Angina pectoris (*see section 4.4*)	Less frequent	-
Myocardial infarction possibly secondary to excessive hypotension in high-risk patients (*see section 4.4*)	Less frequent	Less frequent
Dysrhythmia including bradycardia, ventricular tachycardia, atrial fibrillation	Less frequent	Frequent
Vascular disorders		
Flushing	-	Frequent
Hypotension (and effects related to hypotension) (*see section*	Frequent	Frequent

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4.4)		
Vasculitis	Less frequent	Frequent
Raynaud's phenomenon	Not known	-
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Frequent	Frequent
Cough (*see section 4.4*)	Frequent	Frequent
Bronchospasm	Frequent	-
Eosinophilic pneumonia	Less frequent	-
Gastrointestinal disorders		
Gingival hyperplasia	-	Less frequent
Abdominal pain	Frequent	Frequent
Nausea	Frequent	Frequent
Vomiting	Frequent	Frequent
Dyspepsia	Frequent	Frequent
Changes of bowel habit	-	Frequent
Dry mouth	Frequent	Frequent
Diarrhoea	Frequent	Frequent
Constipation	Frequent	Frequent
Pancreatitis	Less frequent	Frequent
Gastritis	-	Less frequent
Hepato-biliary disorders		
Hepatitis, jaundice (*see section 4.4*)	-	Less frequent
Hepatitis either cytolitic or cholestatic (*see section 4.4*)	Less frequent	-
Hepatic enzymes increased (mostly consistent with	-	Less frequent

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cholestasis)		
Skin and subcutaneous tissue disorders		
Quincke's oedema	-	Less frequent
Erythema multiforme	Less frequent	Less frequent
Alopecia	-	Frequent
Purpura	-	Frequent
Skin discolouration	-	Frequent
Hyperhidrosis	Frequent	Frequent
Pruritus	Frequent	Frequent
Rash exanthema	Frequent	Frequent
Urticaria (*see section 4.4*)	Frequent	Frequent
Photosensitivity reactions	Frequent	Less frequent
Pemphigoid	Frequent	-
Psoriasis aggravation	Less frequent	-
Stevens-Johnson syndrome	-	Less frequent
Toxic epidermal necrolysis	-	Not known
Musculoskeletal and connective tissue disorders		
Joint swelling (ankle swelling)	-	Frequent
Arthralgia	Frequent	Frequent
Myalgia	Frequent	Frequent
Muscle spasms	Frequent	Frequent
Back pain	-	Frequent
Muscular cramps	Frequent	Frequent
Renal and urinary disorders		

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Renal impairment	Frequent	-
Renal failure acute	Less frequent	-
Micturition disorder, pollakiuria, nocturia	-	Frequent
Reproductive system and Breast disorders		
Erectile dysfunction	Frequent	Frequent
Gynaecomastia	-	Frequent
General disorders and administration site conditions		
Oedema	-	Frequent
Oedema peripheral	Frequent	-
Fatigue	-	Frequent
Atypical chest pain	Frequent	Frequent
Asthenia	Frequent	Frequent
Pain	-	Frequent
Malaise	Frequent	Frequent
Pyrexia	Frequent	-
Investigations		
Weight gain, weight decrease	-	Frequent
Blood urea increased	Frequent	-
Blood creatinine increased	Frequent	-
Blood bilirubin increased	Rare Less frequent	-
Hepatic enzyme increased	Rare Less frequent	-
Haemoglobin decreased and haematocrit decreased	Less frequent	-

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Injury, Poisoning and Procedural Complications		
Fall	Frequent	-

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 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

Related to perindopril component

There is no information on overdose with **AMLESSA** in humans.

For amlodipine, experience with intentional overdose in humans is limited. Large overdosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Any hypotension due to amlodipine overdosage calls for a monitoring in cardiologic intensive care unit. 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. 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. Amlodipine is not dialyzable.

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

renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. The recommended treatment of overdose is intravenous infusion of normal saline 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

A7.1.3 Other hypotensives

Mechanism of action

Perindopril

Perindopril is an inhibitor of the enzyme that convert 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 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 system (and thus also activation of the prostaglandin system). It is possible that this

mechanism contributes to the blood pressure-lowering action of the 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 the 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 anti-hypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: though effects are about 75 – 100 % of peak effects.

In responding patients, the maximum anti-hypertensive effects is achieved within a month and persist without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to rebound effects.

Amlodipine

Amlodipine is a dihydropyridine calcium channel antagonist, it produces its effects by binding to the α_1 subunit of the L-type calcium channels and reducing calcium flux through the channel. Binding of amlodipine results in a marked decrease in transmembrane calcium current causing long lasting relaxation of smooth muscle and reduction in contractility in cardiac muscle throughout the heart and decreases in sinus node pacemaker rate and atrioventricular node conduction velocity.

Amlodipine decreases myocardial contractile force thereby reducing myocardial oxygen requirements, in arterial smooth muscle calcium channel block decreases arterial and intraventricular pressure. It reduces coronary vascular resistance leading to an increase in coronary

blood flow. Vascular smooth muscle is relaxed at lower concentrations than those required for prominent direct effects on the heart. Arteriolar resistance and blood pressure are thus lowered, contractility and segmental ventricular function are improved and heart rate and cardiac output are moderately increased.

5.2 Pharmacokinetic properties

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

Pharmacokinetics of AMLESSA

Pharmacokinetics of Perindopril

Absorption

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

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

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

Distribution

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

Elimination

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

Elderly, Heart Failure, Renal Failure

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.

Hepatic impairment

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

Pharmacokinetics of Amlodipine

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

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 the 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 %.

5.3 Preclinical safety data

N/A

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline

Magnesium stearate

Silica, colloidal anhydrous

Sodium hydrogen carbonate

Sodium starch glycolate

Starch, pregelatinized

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Store at or below 25 °C.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

Blister pack (OPA/Aluminium/PVC/Alu foil) in a carton box.

28, 30, 50, 60, 90 and 100 tablets, in a carton box.

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Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

LHC Pharmaceuticals (Pty) Ltd

553 Willow Park Manor

33 Ghaap Street

Pretoria, South Africa

8. REGISTRATION NUMBER(S)

AMLESSA 4 mg/5 mg – 54/7.1/0757

AMLESSA 4 mg/10 mg – 54/7.1/0758

AMLESSA 8 mg/5 mg – 54/7.1/0759

AMLESSA 8 mg/10 mg – 54/7.1/0760

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 November 2022

10. DATE OF REVISION OF THE TEXT