# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Dalnecombi 7 mg/5 mg/2.5 mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 7 mg perindopril arginine (equivalent to 4.75 mg perindopril), amlodipine besilate equivalent to 5 mg amlodipine and 2.5 mg indapamide.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

White or almost white, round (8 mm in diameter), biconvex tablet, marked with K4 on one side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

Posology

One Dalnecombi tablet per day, preferably to be taken in the morning and before a meal.
The fixed dose combination 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)*
Dalnecombi is contraindicated in patients with severe renal impairment (creatinine clearance below 30 ml/min).
The usual medical follow-up includes monitoring of creatinine and potassium.

*Hepatic impairment (see sections 4.3 and 4.4)*
Dalnecombi is contraindicated in patients with severe hepatic impairment.

*Elderly (see section 4.4 and 5.2)*
Elderly patients can be treated with Dalnecombi when renal function is normal or only minimally impaired. The usual medical follow-up should include monitoring of creatinine and potassium.

*Paediatric population*
The safety and efficacy of Dalnecombi in children and adolescents have not been established. No data are available.

Method of administration

Oral use.

### 4.3 Contraindications

- Hypersensitivity to the active substances, to ACE inhibitors, to dihydropyridines derivatives, to other sulfonamides or to any of the excipients listed in section 6.1,
- Severe renal impairment (creatinine clearance below 30 ml/min) (see sections 4.2 and 4.4),
- Hepatic encephalopathy or severe impairment of liver function,
- Hypokalaemia,
- History of angioedema associated with previous ACE inhibitor therapy (see section 4.4),
- Hereditary or idiopathic angioedema,
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6),
- 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 of Dalnecombi with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 $m^2$) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Dalnecombi 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),
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney (see section 4.4).

**4.4 Special warnings and precautions for use**

*Special warnings*

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

*Hypersensitivity/Angioedema*
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see section 4.8). This may occur at any time during therapy. In such cases, Dalnecombi 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 adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving Dalnecombi (see section 4.3).
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see section 4.8).

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of Dalnecombi. If treatment with sacubitril/valsartan is stopped, Dalnecombi must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).
Concomitant use of ACE inhibitors with NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE inhibitor.

*Anaphylactoid reactions during desensitisation*

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

*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. Dalnecombi 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 Dalnecombi is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

*Dual blockade of the renin-angiotensin-aldosterone system (RAAS)*
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

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

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

*Primary aldosteronism*
Patients with primary hyperaldosteronism generally will not respond to anti-hypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

*Pregnancy*
Dalnecombi should not be initiated during pregnancy. Unless continued Dalnecombi is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with Dalnecombi should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

*Renal impairment*
Dalnecombi is contra-indicated in patients with severe renal impairment (creatinine clearance below 30 ml/min) (see section 4.3).
The usual medical follow-up should include monitoring of potassium levels and creatinine (see section 4.2).
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment.

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

Thiazide and related diuretics are fully effective only when renal function is normal or only minimally impaired (plasma creatinine below levels of the order of 25 mg/l, i.e. 220 µmol/l in an adult). In the elderly, this plasma creatinine must be adjusted in relation to age, weight and gender.

Hypovolaemia, secondary to the loss of water and sodium induced by the diuretic at the start of treatment causes a reduction in glomerular filtration. This may lead to an increase in blood urea and plasma creatinine. This transitory functional renal insufficiency is of no consequence in individuals with normal renal function but may worsen pre-existing renal insufficiency.

*Kidney transplantation*

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

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

*Hepatic impairment*
When liver function is impaired, thiazide-related diuretics may cause, particularly in case of electrolyte imbalance, hepatic encephalopathy which can progress to hepatic coma. Administration of
Dalnecombi should be stopped immediately if this occurs.

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood.
The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function.

Patients receiving Dalnecombi who develop jaundice, marked elevations of hepatic enzymes or hepatic encephalopathy should discontinue Dalnecombi and receive appropriate medical follow- up (see section 4.8).

*Elderly*
Renal function and potassium levels should be tested before the start of treatment. The medical follow- up should include monitoring of potassium and creatinine (see sections 4.2 and 5.2).

*Precautions for use*

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

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

*Hypotension and water and sodium depletion*
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 Dalnecombi.
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.

Plasma sodium must be measured before starting treatment, then at regular intervals subsequently. The fall in plasma sodium may be asymptomatic initially and regular monitoring is therefore essential, and should be even more frequent in the elderly and cirrhotic patients (see sections 4.8 and 4.9). Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be responsible for dehydration and orthostatic hypotension.
Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis: the incidence and degree of this effect are slight.

*Aortic and mitral valve stenosis / hypertrophic cardiomyopathy*

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

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

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

*Surgery/anaesthesia*
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. Dalnecombi 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.

*Diabetic patients*
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with Dalnecombi, in particular in the presence of hypokalaemia (see section 4.5).

*Potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes*
The combination of Dalnecombi and potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes is not recommended (see section 4.5).

*Hyperkalaemia*
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril, ACE inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride, alone or in combination), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole, other ACE inhibitors, angiotensin-II antagonists, acetylsalicylic acid ≥ 3 g/day, COX-2 inhibitors and non-selective NSAIDs, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim) and 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. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored. If concomitant use of Dalnecombi and any of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

*Hypokalaemia*
Potassium depletion with hypokalaemia is the major risk of thiazide and related diuretics. Hypokalaemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of hypokalaemia (< 3.4 mmol/l) must be prevented in certain high risk populations, i.e. the elderly, malnourished and/or polymedicated, cirrhotic patients with oedema and ascites, coronary artery disease and cardiac failure patients. In this situation, hypokalaemia increases the cardiac toxicity of digitalis preparations and the risks of arrhythmias.

Individuals with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as well as bradycardia, is then a predisposing factor to the onset of severe arrhythmias, in particular, potentially fatal torsades de pointes.

More frequent monitoring of plasma potassium is required in all the situations indicated above. The first measurement of plasma potassium should be obtained during the first week following the start of treatment.

Detection of hypokalaemia requires its correction. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.

*Hypercalcaemia*
Thiazide and related diuretics may decrease urinary calcium excretion and cause a slight and transitory rise in plasma calcium. Frank hypercalcaemia may be due to previously unrecognised hyperparathyroidism.

Treatment should be withdrawn before the investigation of parathyroid function.

*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).

*Choroidal effusion, acute myopia and secondary angle-closure glaucoma*
Sulfonamide or sulfonamide derivative drugs 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 drug 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 sulfonamide or penicillin allergy.

*Uric acid*
Tendency to gout attacks may be increased in hyperuricaemic patients.

*Athletes*
Athletes should note that this product contains an active substance which may cause a positive reaction in doping tests.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

**4.5 Interaction with other medicinal products and other forms of interaction**

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

*Drugs 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).

*Drugs inducing hyperkalaemia*

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with Dalnecombi. Some drugs or therapeutic classes may increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), ACE inhibitors, angiotensin-II receptors antagonists, NSAIDs, heparins, immunosuppressant agents such as ciclosporin or tacrolimus, trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. The combination of Dalnecombi with these drugs increases the risk of hyperkalaemia. Therefore, the combination of Dalnecombi with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

*Concomitant use contra-indicated (see section 4.3):*

Aliskiren

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

Extracorporeal treatments
Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran 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.

*Concomitant use not recommended (see section 4.4)*

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

Estramustine
Risk of increased adverse effects such as angioneurotic oedema (angioedema).

Potassium-sparing diuretics (e.g. triamterene, amiloride), potassium (salts)
Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). ACE inhibitors must not be associated with hyperkalaemic substances, except in hypokalaemia.
The combination of Dalnecombi with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see below.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Use of Dalnecombi with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

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

*Concomitant use requiring precautions for use*

Torsades de pointes-inducing drugs such as but not limited to

- class Ia antiarrhythmic agents (e.g. quinidine, hydroquinidine, disopyramide),
- class III antiarrhythmic agents (e.g. amiodarone, sotalol, dofetilide, ibutilide, bretylium),
- some antipsychotics:
- phenothiazines (e.g. chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (e.g. amisulpride, sulpiride, sultopride, tiapride),
- butyrophenones (e.g. droperidol, haloperidol), other antipsychotic (e.g pimozide),
- others substances: (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrine, mizolastine, pentamidine, sparfloxacin, moxifloxacin, vincamine IV, methadone, astemizole, terfenadine).

Increased risk of ventricular arrhythmias, particularly *torsades de pointes* (hypokalaemia is a risk factor).

Monitor for hypokalaemia and correct, if required, before introducing this combination. Clinical, plasma electrolytes and ECG monitoring.
Use substances which do not have the disadvantage of causing torsades de pointes in the presence of hypokalaemia.

Other compounds causing hypokalaemia: amphotericin B (IV), gluco- and mineralo-corticoids (systemic route), tetracosactide, stimulant laxatives

Increased risk of hypokalaemia (additive effect).
Monitoring of plasma potassium and correction if required. Must be particularly borne in mind in case of concomitant digitalis treatment. Use non-stimulant laxatives.

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

Baclofen
Increased antihypertensive effect. Monitor blood pressure, renal function and adapt antihypertensive dosage if necessary.

Non-potassium-sparing diuretics
Patients on diuretics, and especially those who are volume and/or salt depleted, m ay 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 Dalnecombi.
In arterial hypertension, when prior diuretic therapy can have caused salt/volume depletion, the diuretic must be discontinued before initiating Dalnecombi in which case a non-potassium-sparing diuretic can be thereafter reintroduced.
Renal function (creatinine levels) must be monitored during the first few weeks of Dalnecombi therapy.

Potassium-sparing diuretics (eplerenone, spironolactone, triamterene, amiloride)
With eplerenone or spironolactone at doses between 12.5 mg to 50 mg by day and with low doses of ACE inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction <40%, and previously treated with ACE inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.
Before initiating the combination, check the absence of hyperkalaemia and renal impairment.
A close monitoring of the kalaemia and creatininemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Whilst rational combinations are useful in some patients, hypokalaemia or hyperkalaemia particularly in patients with renal failure or diabetes may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥ 3 g/day
When ACE-inhibitors and indapamide 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 Dalnecombi 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.

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 Dalnecombi 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.

Digitalis preparations

Hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digitalis. Monitoring of plasma potassium, magnesium and ECG is recommended and, if necessary, adjusting the treatment.

Allopurinol
Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

*Concomitant use which requires some care*

Antihypertensive agents (such as beta-blockers), vasodilatators, imipramine-like antidepressants and neuroleptics
Concomitant use of these agents may increase the hypotensive effects of Dalnecombi and risk of orthostatic hypotension (additive effect).

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

Metformin
Increased risk of metformin induced lactic acidosis due to the possibility of functional renal failure associated with diuretics and more particularly with loop diuretics. Do not use metformin when plasma creatinine exceeds 15 mg/l (135 µmol/l) in men and 12 mg/l (110 µmol/l) in women.

Tricyclic antidepressants/Antipsychotics/Anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with Dalnecombi may result in further reduction of blood pressure.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of Dalnecombi.

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

Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin)
Increased antihypertensive effect and increased risk of orthostatic hypotension.

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.

Amifostine
May potentiate the antihypertensive effect of amlodipine.

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

Iodinated contrast media
In the presence of dehydration caused by diuretics, increased risk of acute renal failure, in particular when large doses of iodinated contrast media are used.
Rehydration before administration of the iodinated compound.

Calcium (salts)
Risk of hypercalcaemia resulting from decreased urinary elimination of calcium.

Tacrolimus
There is a risk of increased tacrolimus blood levels when co administered with amlodipine and of increased plasma creatinine without any change in circulating ciclosporin levels, even in the absence of water/sodium depletion, when co administered with indapamide.

In order to avoid toxicity of tacrolimus, administration of Dalnecombi in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Ciclosporin
Risk of increased plasma creatinine without any change in circulating ciclosporin levels when co administered with indapamide, even in the absence of water/sodium depletion.

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

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

**4.6 Fertility, pregnancy and lactation**

Given the effects of the individual components in this combination product on pregnancy and lactation:
Dalnecombi is not recommended during the first trimester of pregnancy. Dalnecombi is contraindicated during the second and third trimesters of pregnancy.

Dalnecombi is not recommended during breast-feeding. A decision should therefore be made whether to discontinue nursing or to discontinue Dalnecombi taking account the importance of this therapy for the mother.

Pregnancy

*Linked to perindopril*

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).
Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

*Linked to 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 foeto-placental ischaemia and growth retardation. Moreover, rare 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).

Breastfeeding

Dalnecombi is not recommended during breast-feeding.

*Linked to 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 breast - feeding are preferable, especially while nursing a newborn or preterm infant.

*Linked to 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.

*Linked to indapamide*
There is insufficient information on the excretion of indapamide/metabolites in human milk. Hypersensitivity to sulfonamide-derived medicines and hypokalaemia might occur. A risk to the newborns/infants cannot be excluded. Indapamide is closely related to thiazide diuretics which have been associated, during breast-feeding, with decreased or even suppression of milk lactation.

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.

*Linked to amlodipine*
Reversible biochemical changes in the head of spermatozoa have been reported in some patient s 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 Dalnecombi on the ability to drive and use machines have been performed.

Perindopril, amlodipine and indapamide 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.

As a result the ability to drive vehicles or to operate machinery may be impaired. Caution is recommended with Dalnecombi especially at the start of treatment.

**4.8 Undesirable effects**

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

Tabulated list of adverse reactions
The following undesirable effects have been observed during treatment with perindopril, amlodipine or indapamide given separately and ranked under the MedDRA classification by body system and under the following frequency:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1 000 to < 1/100)
- Rare (≥ 1/10 000 to < 1/1 000)
- Very rare (< 1/10 000)
- Not known (cannot be estimated from the available data)

| MedDRA System Organ Class | Undesirable Effects | Frequency | | |
|---|---|---|---|---|
| | | Perindopril | Amlodipine | Indapamide |
| **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 |
| | Aplastic anaemia | - | - | Very rare |
| | Pancytopenia | 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 | - | Very rare | Common |
| **Metabolism and Nutrition Disorders** | Hypokalaemia (see section 4.4) | - | - | Common |
| | Hypoglycaemia (see sections 4.4 and 4.5) | Uncommon * | - | - |
| | Hyperkalaemia reversible on discontinuation (see section 4.4) | Uncommon * | - | - |
| | Hyponatraemia (see section 4.4) | Uncommon * | - | Uncommon |
| | Hypochloraemia | - | - | Rare |
| | Hypomagnesaemia | - | - | Rare |
| | Hyperglycaemia | - | Very rare | Not known |
| | 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 (especially at the beginning of the treatment) | Common | Common | - |
| | Headache (especially at the beginning of the treatment | Common | Common | Rare |
| | Paraesthesia | Common | Uncommon | Rare |
| | Somnolence (especially at the beginning of the treatment) | Uncommon * | Common | - |
| | Hypoaesthesia | - | Uncommon | - |
| | Dysgeusia | Common | Uncommon | - |
| | Tremor | - | Uncommon | - |
| | Syncope | Uncommon * | Uncommon | Not known |
| | Hypertonia | - | Very rare | - |
| | Neuropathy peripheral | - | Very rare | - |
| | Stroke possibly secondary to excessive hypotension in | Very rare | - | - |

| | | | | |
|---|---|---|---|---|
| | high- risk patients (see section 4.4) | | | |
| | Extrapyramidal disorder | - | Not known | - |
| | (extrapyramidal syndrome) | | | |
| **Eye Disorders** | Visual impairment | Common | Common | Not known |
| | 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 | - | - |
| | Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) | Very rare | Uncommon | Very rare |
| | 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 hypotension) (see section 4.4) | Common | Uncommon | Very rare |
| | Vasculitis | Uncommon* | Very rare | - |
| | Raynaud's phenomenon | Not known | - | - |
| **Respiratory, Thoracic and Mediastinal Disorders** | Cough | Common | Uncommon | - |
| | Dyspnoea | Common | Common | - |
| | Bronchospasm | Uncommon | - | - |
| | Eosinophilic pneumonia | Very rare | - | - |
| **Gastro-intestinal Disorders** | Abdominal pain | Common | Common | - |
| | Constipation | Common | Common | Rare |
| | Diarrhoea | Common | Common | - |
| | Dyspepsia | Common | Common | - |
| | Nausea | Common | Common | Rare |
| | Vomiting | Common | Uncommon | Uncommon |
| | Dry mouth | Uncommon | Uncommon | Rare |
| | Change of bowel habit | - | Common | - |
| | Gingival hyperplasia | - | Very rare | - |
| | Pancreatitis | Very rare | Very rare | Very rare |
| | Gastritis | - | Very rare | - |

| | | | | |
|---|---|---|---|---|
| **Hepato-biliary Disorders** | Hepatitis either cytolitic or cholestatic (see section 4.4) | Very rare | Very rare | Not known |
| | Jaundice | - | Very rare | - |
| | Hepatic function abnormal | - | - | Very rare |
| | Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see sections 4.3 and 4.4) | - | - | Not known |
| **Skin and Subcutaneous Tissue Disorders** | Pruritus | Common | Uncommon | - |
| | Rash | Common | Uncommon | - |
| | Exanthema | - | Uncommon | - |
| | Rash maculo-papular | - | - | Common |
| | Urticaria (see section 4.4) | Uncommon | Uncommon | Very rare |
| | Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4) | Uncommon | Very rare | Very rare |
| | Alopecia | - | Uncommon | - |
| | Purpura | - | Uncommon | Uncommon |
| | Skin discolouration | - | Uncommon | - |
| | Hyperhidrosis | Uncommon | Uncommon | - |
| | Photosensitivity reaction (see section 4.4) | Uncommon * | Very rare | Not known |
| | Pemphigoid | Uncommon * | - | - |
| | Psoriasis aggravation | Rare | - | - |
| | Erythema multiforme | Very rare | Very rare | - |
| | Stevens-Johnson Syndrome | - | Very rare | Very rare |
| | Exfoliative dermatitis | - | Very rare | - |
| | Toxic epidermal necrolysis | - | Not known | Very rare |
| | Quincke's oedema | - | Very rare | - |
| **Musculoskeletal and Connective Tissue Disorders** | Muscle spasms | Common | Common | Not known |
| | Joint swelling (ankle swelling) | - | Common | - |
| | Arthralgia | Uncommon * | Uncommon | - |
| | Muscular weakness | - | - | Not known |
| | Myalgia | Uncommon * | Uncommon | Not known |
| | Rhabdomyolysis | - | - | Not known |
| | Back pain | - | Uncommon | - |
| | Possible worsening of pre-existing acute disseminated 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** | Erectile dysfunction | Uncommon | Uncommon | Uncommon |

| | | | | |
|---|---|---|---|---|
| **System and Breast Disorders** | | | | |
| | Gynaecomastia | - | Uncommon | - |
| **General Disorders and Administration Site Conditions** | Asthenia | Common | Common | - |
| | Fatigue | - | Common | Rare |
| | Oedema | - | Very common | - |
| | Oedema peripheral | Uncommon* | - | - |
| | Chest pain | Uncommon * | Uncommon | - |
| | Pain | - | Uncommon | - |
| | Malaise | Uncommon * | Uncommon | - |
| | Pyrexia | Uncommon* | - | - |
| **Investigations** | Weight increase | - | Uncommon | - |
| | Weight decrease | - | Uncommon | - |
| | Blood urea increased | Uncommon* | - | - |
| | Blood creatinine increased | Uncommon* | - | - |
| | Blood bilirubin increased | Rare | - | - |
| | Hepatic enzyme increased | Rare | Very rare | Not known |
| | Haemoglobin decreased and haematocrit decreased (see section 4.4) | Very rare | - | - |
| | Electrocardiogram QT prolonged (see sections 4.4 and 4.5) | - | - | Not known |
| | Blood uric acid increased | - | - | 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 1.5 mg and 2.5 mg, plasma potassium analysis showed a dose-dependent effect of indapamide:

- Indapamide 1.5 mg: 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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

**4.9 Overdose**

There is no experience of overdose with Dalnecombi.

*Perindopril*
Limited data are available for overdosage in humans.

Symptoms
Associated with the overdosage of ACE inhibitors symptomy may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

Treatment
The recommended treatment of overdosage 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.

*Amlodipine*
Experience with intentional overdose in humans is limited.

Symptoms
Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment
Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.
A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

*Indapamide*

Symptoms
Indapamide has been found free of toxicity at up to 40 mg, i.e. 16 times the therapeutic dose.
Signs of acute poisoning take the form above all of water/electrolyte disturbances (hyponatraemia, hypokalaemia). Clinically, possibility of nausea, vomiting, hypotension, cramps, vertigo, drowsiness, confusion, polyuria or oliguria possibly to the point of anuria (by hypovolaemia).

Treatment
Initial measures involve the rapid elimination of the ingested substance(s) by gastric wash-out and/or administration of activated charcoal, followed by restoration of water/electrolyte balance to normal in a specialised centre.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors, other combinations, ATC code: C09BX01

Dalnecombi 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, amlodipine, a calcium ion flux inhibitor of the dihydropyridine group and indapamide, a chlorosulphamoyl diuretic.
The pharmacological properties of Dalnecombi are derived from those of each of the components taken separately. The combination of these substances has an additive antihypertensive effect.

Mechanism of action

*Perindopril*
Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein- kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).
Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro.

*Amlodipine*
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

*Indapamide*
Indapamide is a non-thiazide sulfonamide with an indole ring, belonging to the diuretic family. At the dose of 2.5 mg per day, indapamide exerts a prolonged antihypertensive activity in hypertensive human subjects.

Pharmacodynamic effects

*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 ven tricular 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.

*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.

*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 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.

Clinical efficacy and safety:

*Perindopril/amlodipine*
ASCOT-BPLA trial was designed to compare 2 antihypertensive treatment strategies (amlodipine ± perindopril vs atenolol ± bendroflumethiazide) in the prevention of coronary heart disease events in 19,257 hypertensive patients who have no history of coronary heart disease and at least 3 others CV risk factors.
The primary end-point was the combined of non-fatal myocardial infarction and fatal coronary heart disease. The study was stopped early due to a significant reduction in mortality in the amlodipine arm as compared to the atenolol arm.
The amlodipine ± perindopril regimen did lower brachial blood pressure more effectively than the atenolol-based regimen, with a mean in-trial systolic difference of 2.7 mmHg ($p<0.0001$) and diastolic difference of 1.9 mmHg ($p<0.0001$). Compared with atenolol based regimen, amlodipine ± perindopril reduced the risk of non-fatal myocardial infarction (MI) + fatal coronary heart disease by 10%, when including silent MI by 13% ($p=0.04$); coronary events by 13% ($p=0.007$); cardiovascular events and procedures by 16% 23 ($p<0.0001$); all-cause mortality by 11% ($p=0.02$); cardiovascular mortality by 24% ($p=0.001$); fatal and non-fatal stroke by 23% ($p=0.0003$); development of diabetes mellitus by 30% ($p<0.0001$); development of renal impairment by 15% ($p=0.02$); fatal and non-fatal heart failure by 16% (NS).

In a 6-month, multicentre, randomised, double-blind, active-controlled study, 1 774 patients with mild to moderate hypertension received either perindopril 3.5 mg/amlodipine 2.5 mg, uptitrated to 7 mg/5 mg, and 14 mg/10 mg, then to 14 mg/10 mg combined with indapamide 1.5 mg, or a valsartan- amlodipine strategy (valsartan 80 mg uptitrated to 160 mg and to valsartan/amlodipine 160 mg/5 mg, then to valsartan/amlodipine160 mg/10 mg).
At 3 months, the perindopril/amlodipine strategy showed clinically and statistically significant mean decrease in SBP/DBP (25.9/16.9 mmHg) as compared to valsartan-amlodipine strategy (23.6/15.5 mmHg) ($p<0.001$ for all comparisons).
Blood pressure was controlled in 56.4% of patients treated with the perindopril/amlodipine strategy versus 49.0% with valsartan-amlodipine strategy ($p=0.002$), and the rate of responders was 87.4% versus 81.6%, respectively ($p<0.001$).
The superiority of the perindopril/amlodipine strategy over the valsartan-amlodipine strategy on blood pressure decrease and responder rates was observed from1 month and maintained at each visit up to 6 months.
These results were confirmed in a 24-hour automated blood pressure monitoring (ABPM) performed in a subset of 1 029 patients. At 3 months and 6 months, the decrease of the mean SBP and DBP over 24 hours was greater with the perindopril/amlodipine strategy (15.5/9.4 mmHg and 17/10.4 mmHg, respectively) as compared to valsartan-amlodipine strategy (12.7/8.0 mmHg and 14.7/9.2 mmHg, respectively) ($p\leq0.001$).
In the 8-month open-label follow-up on 1 554 patients, the safety profile of perindopril/amlodipine was in line with the safety profiles of perindopril and amlodipine.

In a 9-month multicentre, randomised, double-blind, active-controlled study, 3 270 patients with mild to severe hypertension received either perindopril /amlodipine 3.5 mg/2.5 mg, uptitrated to 7 mg/5 mg, 14 mg/5 mg then 14 mg/10 mg, or an irbesartan-hydrochlorothiazide strategy (irbesartan 150 mg, then irbesartan/hydrochlorothiazide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg).
The proportion of patients with controlled blood pressure statistically significantly increased with each of the perindopril/amlodipine treatment dose over each evaluation period ($p<0.001$ until 3 months, and $p\leq0.003$ until 6 months).
After 6 months of treatment, the mean decrease in blood pressure was similar in the perindopril/amlodipine group (22.0/10.1 mmHg) and the irbesartan-hydrochlorothiazide group (22.5/9.6 mmHg) for both SBP ($p=0.116$) and DBP ($p=0.050$).

The most common adverse reactions in clinical trials were dizziness, cough and oedema.

The adverse reactions reported in clinical trials were in agreement with those anticipated from the safety profiles of the components perindopril and amlodipine.

*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 f or 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 g once a day. Only 34% of the subjects remained treated with perindopril tert-butylamine 2 mg (equivalent to 2.5 mg perindopril arginine)/indapamide 0.625 mg (versus 20% with enalapril 10 mg).

At the end of treatment, LVMI had decreased significantly more in the perindopril/indapamide group (-10.1 g/m$^2$) than in the enalapril group (-1.1 g/m$^2$) 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, 2x2 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 tot al 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 randomized 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 randomized 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 Dalnecombi in children.
The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing perindopril arginine/amlodipine/indapamide in all subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use).

**5.2 Pharmacokinetic properties**

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

*Perindopril*

Absorption
After oral administration, the absorption of perindopril is rapid and the peak concentration is reached within 1 hour. The plasma half-life of perindopril is equal to 1 hour.
Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours.

As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.
It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure.

Distribution
The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

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

*Amlodipine*

Absorption, distribution, plasma protein binding

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

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

*Indapamide*

Absorption
Indapamide is rapidly and completely absorbed after oral administration. Peak blood levels are obtained after 1 to 2 hours.

Distribution
Indapamide is concentrated in the erythrocytes and is 79% bound to plasma protein and to erythrocytes. It is taken up by the vascular wall in smooth vascular muscle according to it s high lipid solubility.

Biotransformation, elimination
70% of a single oral dose is eliminated by the kidneys and 23% by the gastrointestinal tract. Indapamide is metabolised to a marked degree with 7% of the unchanged product found in the urine during the 48 hours following administration. Elimination half-life (β phase) of indapamide is approximately 15 – 18 hours.

Special populations

*Paediatric population (age below 18 years)*
No pharmacokinetic data are available in the paediatric population.

*Elderly*
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Initiation should take place with care in older people depending on renal function.
Elimination of perindoprilat is decreased in the elderly. Renal function should be monitored. Therefore, the usual medical follow-up will include monitoring of creatinine and potassium (see sections 4.2 and 4.4).

*Hepatic impairment*
Caution should be exercised in patients with liver disease (see sections 4.2 and 4.4).
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.
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).

**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 sh own to induce adverse effects on late foetal development, resulting in foetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed. No carcinogenicity has been observed in long term studies in rats and mice. Fertility was not impaired either in male or in female rats.

*Amlodipine*

Reproductive toxicology
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.

Impairment of fertility
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.

Carcinogenesis, mutagenesis
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

*Indapamide*
The highest doses administered orally to different animal species (40 to 8000 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 intravenou sly or intraperitoneally were related to the pharmacological action of indapamide, i.e. bradypnoea and peripheral vasodilation.
Reproductive toxicity studies have not shown embryotoxicity and teratogenicity. Fertility was not impaired either in male or in female rats.
Indapamide has been tested negative concerning mutagenic and carcinogenic properties.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Calcium chloride hexahydrate
Microcrystalline cellulose
Pregelatinised maize starch
Sodium starch glycolate (Type A)
Sodium hydrogen carbonate
Colloidal hydrated sillica
Magnesium stearate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from light and moisture.

### 6.5 Nature and contents of container

oPA/Alu/PVC//Alu blisters containing 10, 30, 60, 90, 100 or 120 tablets, in a box.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements for disposal.

**7 MARKETING AUTHORISATION HOLDER**

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

**8 MARKETING AUTHORISATION NUMBER**

PA1347/117/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 31st January 2025

**10 DATE OF REVISION OF THE TEXT**

August 2025