SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Perindopril Arginine Clonmel 2.5 mg film-coated tablets
Perindopril Arginine Clonmel 5 mg film-coated tablets
Perindopril Arginine Clonmel 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Perindopril Arginine Clonmel 2.5 mg: Each film-coated tablet contains 2.5 mg perindopril arginine equivalent to 1.6975 mg perindopril.
Perindopril Arginine Clonmel 5 mg: Each film-coated tablet contains 5 mg perindopril arginine equivalent to 3.395 mg perindopril.
Perindopril Arginine Clonmel 10 mg: Each film-coated tablet contains 10 mg perindopril arginine equivalent to 6.790 mg perindopril.

Excipient with known effect
Perindopril Arginine Clonmel 2.5 mg: Each film-coated tablet contains 58.19 mg lactose (as monohydrate).
Perindopril Arginine Clonmel 5 mg: Each film-coated tablet contains 116.38 mg lactose (as monohydrate).
Perindopril Arginine Clonmel 10 mg: Each film-coated tablet contains 232.75 mg lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Perindopril Arginine Clonmel 2.5 mg: White to off-white, rounded, convex film-coated tablet of diameter 5.0 ± 0.25 mm.
Perindopril Arginine Clonmel 5 mg: Light-green, oval, biconvex film-coated tablet with length 10.0 ± 0.50 mm and width 4.75 ± 0.24 mm with both-sided score line. The tablet can be divided into equal doses.
Perindopril Arginine Clonmel 10 mg: Green to marble green, rounded, biconvex film-coated tablet of diameter 9.0 ± 0.45 mm with one-sided debossing “10”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of hypertension.

Heart failure (only Perindopril Arginine Clonmel 2.5 mg and 5 mg)
Treatment of symptomatic heart failure.

Stable coronary artery disease
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

4.2 Posology and method of administration

Posology
The dose should be individualised according to the patient profile (see section 4.4) and blood pressure response.

Hypertension
Perindopril Arginine Clonmel may be used in monotherapy or in combination with other classes of antihypertensive therapy (see sections 4.3, 4.4, 4.5 and 5.1).
The recommended starting dose is 5 mg given once daily in the morning.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2.5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 10 mg once daily after 1 month of treatment.
Symptomatic hypotension may occur following initiation of therapy with Perindopril Arginine Clonmel; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with Perindopril Arginine Clonmel (see section 4.4). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Perindopril Arginine Clonmel should be initiated with a 2.5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Perindopril Arginine Clonmel should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

Elderly
In elderly patients treatment should be initiated at a dose of 2.5 mg which may be progressively increased to 5 mg after 1 month then to 10 mg if necessary depending on renal function (see table below).

Symptomatic heart failure (only Perindopril Arginine Clonmel 2.5 mg and 5 mg)
It is recommended that Perindopril Arginine Clonmel, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta-blocker, be introduced under close medical supervision with a recommended starting dose of 2.5 mg taken in the morning. This dose may be increased after 2 weeks to 5 mg once daily if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see section 4.4).
Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with Perindopril Arginine Clonmel. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with Perindopril Arginine Clonmel (see section 4.4).

Stable coronary artery disease
Perindopril Arginine Clonmel should be introduced at a dose of 5 mg once daily for 2 weeks, then increased to 10 mg once daily, depending on renal function and provided that the 5 mg dose is well tolerated.
Elderly patients should receive 2.5 mg once daily for 1 week, then 5 mg once daily the next week, before increasing the dose up to 10 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

Special population

Renal impairment

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

Table 1: dosage adjustment in renal impairment

Creatinine clearance (ml/min)	Recommended dose
$Cl_{Cr} \geq 60$	5 mg per day
$30 < Cl_{Cr} < 60$	2.5 mg per day
$15 < Cl_{Cr} < 30$	2.5 mg every other day
Haemodialysed patients*	
$Cl_{Cr} < 15$	2.5 mg on the day of dialysis

* Dialysis clearance of perindoprilat is 70 ml/min.

For patients on haemodialysis, the dose should be taken after dialysis.

Hepatic impairment

No dosage adjustment is necessary in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of perindopril in children and adolescents aged below 18 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Therefore, use in children and adolescents is not recommended.

Method of administration

For oral use. Perindopril Arginine Clonmel is recommended to be taken once daily in the morning before a meal.

4.3 Contraindications

- Hypersensitivity to the active substance, any other ACE inhibitor or to any of the excipients listed in section 6.1.
- 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).
- The concomitant use of Perindopril Arginine Clonmel with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).
- Concomitant use with sacubitril/valsartan therapy. Perindopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5).
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney (see section 4.4).

4.4 Special warnings and precautions for use

Stable coronary artery disease

If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

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 with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see sections 4.2 and 4.8). 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. In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril arginine. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Perindopril Arginine Clonmel may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy

As with other ACE inhibitors, perindopril arginine 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.

Renal impairment

In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient's creatinine clearance (see section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see section 4.8).

In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

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. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Perindopril Arginine Clonmel therapy.

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 arginine has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Perindopril Arginine Clonmel may be required.

Haemodialysis patients

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

Kidney transplantation

There is no experience regarding the administration of perindopril arginine in patients with a recent kidney transplantation.

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

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 arginine (see section 4.8). This may occur at any time during therapy.
In such cases, Perindopril Arginine Clonmel 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 an ACE inhibitor (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.
Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3). Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of perindopril. Treatment with perindopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).
Concomitant use of ACE inhibitors with neprilysin (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 for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting neprilysin (NEP) inhibitors (e.g. 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 low-density lipoproteins (LDL) apheresis
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of

hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see section 4.8).

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. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, 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).

Race
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, perindopril 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 inhibitors. 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 arginine may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued 1 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 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), 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) 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 the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

Lithium
The combination of lithium and perindopril is generally not recommended (see section 4.5).

Potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes
The combination of perindopril and potassium-sparing drugs, potassium supplements or potassium-containing salt substitutes is generally not recommended (see section 4.5).
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 antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of this product is not recommended.

Pregnancy
ACE inhibitors should not be initiated during pregnancy. 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 (see sections 4.3 and 4.6).

Excipients
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, 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 perindopril. 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 these drugs increases the risk of hyperkalaemia. Therefore, the combination of perindopril 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 contraindicated (see section 4.3)

Aliskiren

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

Extracorporeal treatments

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitrile 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.

Concomitant therapy with ACE inhibitor and angiotensin-receptor blocker

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

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).

The combination of perindopril 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 perindopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Concomitant use which requires special care

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 and adapt antihypertensive dosage if necessary.

Non-potassium-sparing diuretics
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating 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. *In diuretic-treated congestive heart failure,* the ACE inhibitor should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic. In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE inhibitor therapy.

Potassium-sparing diuretics (eplerenone, spironolactone)
With eplerenone or spironolactone at doses between 12.5 mg to 50 mg by day and with low doses of ACE inhibitors:
In the treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40%, and previously treated with ACE inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination. Before initiating the combination, check the absence of hyperkalaemia and renal impairment. A close monitoring of the kalaemia and creatininaemia is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including acetylsalicylic acid ≥ 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 ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)
Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

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

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

<u>Concomitant use which requires some care</u>
Antihypertensive agents and vasodilators

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Tricyclic antidepressants/antipsychotics/anaesthetics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 2nd and 3rd 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).

Breast-feeding
Because no information is available regarding the use of perindopril arginine during breast-feeding, Perindopril Arginine Clonmel is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new-born or preterm infant.

Fertility
There was no effect on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines

Perindopril arginine has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.
As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

Summary of the safety profile
The safety profile of perindopril is consistent with the safety profile of ACE inhibitors:

The most frequent adverse events reported in clinical trials and observed with perindopril are: dizziness, headache, paraesthesia, vertigo, visual disturbances, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, diarrhoea, dysgeusia, dyspepsia, nausea, vomiting, pruritus, rash, muscle cramps, and asthenia.

Tabulated list of adverse reactions

The following undesirable effects have been observed during clinical trials and/or post-marketing use with perindopril and ranked under the following frequency: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

MedDRA System Organ Class	Undesirable Effects	Frequency
Blood and the lymphatic system disorders	Eosinophilia	Uncommon*
	Agranulocytosis or pancytopenia	Very rare
	Haemoglobin decreased and haematocrit decreased	Very rare
	Leucopenia/neutropenia	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)	Very rare
	Thrombocytopenia	Very rare
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Rare
Metabolism and nutrition disorders	Hypoglycaemia (see sections 4.4 and 4.5)	Uncommon*
	Hyperkalaemia, reversible on discontinuation (see section 4.4)	Uncommon*
	Hyponatraemia	Uncommon*
Psychiatric disorders	Mood disturbances	Uncommon
	Sleep disorder	Uncommon
	Depression	Uncommon*
Nervous system disorders	Dizziness	Common
	Headache	Common
	Paraesthesia	Common
	Vertigo	Common
	Somnolence	Uncommon*
	Syncope	Uncommon*
	Confusion	Very rare
Eye disorders	Visual disturbances	Common
Ear and labyrinth disorders	Tinnitus	Common
Cardiac disorders	Palpitations	Uncommon*
	Tachycardia	Uncommon*
	Angina pectoris (see section 4.4)	Very rare
	Arrhythmia	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	Very rare
Vascular disorders	Hypotension (and effects related to hypotension)	Common
	Vasculitis	Uncommon*
	Flushing	Rare*

	Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	Very rare
	Raynaud's phenomenon	Not known
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Dyspnoea	Common
	Bronchospasm	Uncommon
	Eosinophilic pneumonia	Very rare
	Rhinitis	Very rare
Gastrointestinal disorders	Abdominal pain	Common
	Constipation	Common
	Diarrhoea	Common
	Dysgeusia	Common
	Dyspepsia	Common
	Nausea	Common
	Vomiting	Common
	Dry mouth	Uncommon
	Pancreatitis	Very rare
Hepatobiliary disorders	Hepatitis either cytolytic or cholestatic (see section 4.4)	Very rare
Skin and subcutaneous tissue disorders	Pruritis	Common
	Rash	Common
	Urticaria (see section 4.4)	Uncommon
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)	Uncommon
	Photosensitivity reactions	Uncommon*
	Pemphigoid	Uncommon*
	Hyperhidrosis	Uncommon
	Psoriasis aggravation	Rare*
	Erythema multiforme	Very rare
Musculoskeletal and connective tissue disorders	Muscle cramps	Common
	Arthralgia	Uncommon*
	Myalgia	Uncommon*
Renal and urinary disorders	Renal insufficiency	Uncommon
	Anuria/oliguria	Rare
	Acute renal failure	Rare*
Reproductive system and breast disorders	Erectile dysfunction	Uncommon
General disorders and administration site condition	Asthenia	Common
	Chest pain	Uncommon*
	Malaise	Uncommon*
	Oedema peripheral	Uncommon*
	Pyrexia	Uncommon*
Investigations	Blood urea increased	Uncommon*
	Blood creatinine increased	Uncommon*
	Blood bilirubin increased	Rare
	Hepatic enzyme increased	Rare
Injury, poisoning and procedural complications	Fall	Uncommon*

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

Clinical trials
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6,122 perindopril patients and 12 (0.2%) of the 6,107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n = 366) versus 2.1% (n = 129) respectively.

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 ADR Reporting, Website: www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

Symptoms
Limited data are available for overdosage in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

Management
The recommended treatment of overdosage is intravenous infusion of sodium chloride 9 mg/ml (0.9%) 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 may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, plain;
ATC code: C09AA04

Mechanism of action
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*.

Clinical efficacy and safety
Hypertension

Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.
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 as a rule, while the glomerular filtration rate (GFR) is usually unchanged.
The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87 – 100 % of peak effects.
The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.
Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy.
In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries.
An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Heart failure (only perindopril arginine 2.5 mg and 5 mg)
Perindopril reduces cardiac work by a decrease in pre-load and after-load. Studies in patients with heart failure have demonstrated

- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2.5 mg of perindopril arginine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.
12,218 patients aged over 18 were randomised to 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) (n = 6,110) or placebo (n = 6,108).
The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.
The main efficacy criterion was the composite of cardiovascular mortality, non-fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – $p < 0.001$).
In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – $p < 0.001$) in the primary endpoint was observed by comparison to placebo.

Paediatric population
The safety and efficacy of perindopril in children and adolescents aged below 18 years have not been established.
In an open, non-comparative clinical study in 62 hypertensive children aged from 2 to 15 years with a glomerular filtration rate> 30 ml/min/1.73 m^2, patients received perindopril with an average dose of 0.07 mg/kg. The dose was individualised according to the patient profile and blood pressure response up to a maximum dose of 0.135 mg/kg/day.
59 patients completed the period of 3 months, and 36 patients completed the extension period of the study, i.e. were followed at least 24 months (mean study duration: 44 months).

Systolic and diastolic blood pressure remained stable from the inclusion to the last assessment in patients previously treated by other antihypertensive treatments, and decreased in naïve patients. More than 75% of children had systolic and diastolic blood pressure below the 95th percentile at their last assessment. The safety was consistent with the known safety profile of perindopril.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) clinical trial data
2 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.

5.2 Pharmacokinetic properties

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 prodrug. 27% of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields 5 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.

Special population
Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).
Dialysis clearance of perindoprilat is equal to 70 ml/min.

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

5.3 Preclinical safety data

In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage. No mutagenicity has been observed in *in vitro* or *in vivo* studies.
Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late 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. Fertility was not impaired either in male or in female rats.
No carcinogenicity has been observed in long term studies in rats and mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Starch, pregelatinized
Sodium starch glycolate
Silica, hydrophobic colloidal
Magnesium stearate

Tablet coating
Hypromellose 2910
Calcium carbonate
Macrogol 3350
Triglycerides, medium chain
Talc

Perindopril Arginine Clonmel 2.5 mg:
Carmellosum
Citric acid

Perindopril Arginine Clonmel 5 mg and 10 mg:
Quinoline yellow aluminium lake (E104)
Iron oxide yellow (E172)
Brilliant blue FCF aluminium lake (E133)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Perindopril Arginine Clonmel 2.5 mg: Store below 25 °C.

Perindopril Arginine Clonmel 5 mg and 10 mg: Store below 25 °C in the original package in order to protect from light.

6.5 Nature and contents of container

OPA/Alu/PVC//Alu or PVC/PVDC white//Alu blisters.

Pack sizes:
Perindopril Arginine Clonmel 2.5 mg: 30 or 90 film-coated tablets
Perindopril Arginine Clonmel 5 mg: 15, 30 or 90 film-coated tablets
Perindopril Arginine Clonmel 10 mg: 30 or 90 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

MA1045/06401
MA1045/06402
MA1045/06403

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Date of first authorisation: 17 January 2024

10. DATE OF REVISION OF THE TEXT

12th April 2024