Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Acerycal 5mg/10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 3.395mg perindopril equivalent to 5mg perindopril arginine and 13.870mg amlodipine besilate equivalent to 10mg amlodipine

Excipient: lactose monohydrate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

Product imported from Poland:
White, square-shaped tablet engraved with 5/10 on one face and on the other face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acerycal is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

4.2 Posology and method of administration

Oral route.
One tablet per day as a single dose, 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 posology is required, the dose of Acerycal could be modified or individual titration with free combination may be considered.

Special populations

Patients with renal impairment and elderly (see sections 4.4 and 5.2)
Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.
Acerycal can be administered in patients with Clcr ≥ 60ml/min, and is not suitable for patients with Clcr < 60ml/min. In these patients, an individual dose titration with the monocomponents is recommended.

Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Patients with hepatic impairment: see sections 4.4 and 5.2
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2).

To find the optimal starting dose and maintenance dose of patients with hepatic impairment, the patients should be individually titrated using the free combination of amlodipine and perindopril. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

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

4.3 Contraindications

Linked to perindopril:
- Hypersensitivity to perindopril or to any other ACE inhibitor,
- History of angioedema associated with previous ACE inhibitor therapy,
- Hereditary or idiopathic angioedema,
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

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

Linked to Acerycal:
All contraindications related to each monocomponent, as listed above, should apply also to the fixed combination of Acerycal.

- Hypersensitivity to any of the excipients.

4.4 Special warnings and precautions for use

All warnings related to each monocomponent, as listed below, should apply also to the fixed combination of Acerycal.

Linked to perindopril

Special warnings
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, Acerycal 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 (see section 4.8).

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.

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. 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).

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitors 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).

Precautions for use

Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients at high risk of symptomatic hypotension, blood pressure, renal function and serum potassium should be monitored closely during treatment with Acerycal.
Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy:
As with other ACE inhibitors, perindopril 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 impairement:
In cases of renal impairment (creatinine clearance < 60 ml/min) an individual dose titration with the monocomponents is recommended (see section 4.2).
Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment (see section 4.8).
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.

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).

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 nonblacks, 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, Acerycal may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkaliemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes mellitus, intercurrent events, in particular dehydratation, 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). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of perindopril and any of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

Linked to amlodipine:

Precautions for use

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

Use in patients with cardiac failure:
Patients with heart failure should be treated with caution.
In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1).
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with impaired hepatic function:
The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

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

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

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

Precautions for use

Excipients:
Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.

Interactions
The concomitant use of Acerycal with lithium, potassium-sparing diuretics or potassium supplements, or dantrolene is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Linked to perindopril

Concomitant use not recommended:

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore the combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium:
Reversible increases in serum lithium concentrations and toxicity (severe neurotoxicity) have been reported during concurrent use of ACE inhibitors. The combination of perindopril with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended (see section 4.4).

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

Concomitant use which requires special care:

Non-steroidal anti-inflammatory medicinal products (NSAIDs) including aspirin ≥ 3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of 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.

Antidiabetic agents (insulin, hypoglycaemic sulphonamides):
The use of angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides. The onset of hypoglycaemic episodes is very rare (there is probably an improvement in glucose tolerance with a resulting reduction in insulin requirements).

Concomitant use to be taken into consideration:

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.

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.

Linked to amlodipine

Concomitant use not recommended:
Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Concomitant use which requires special care:
CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

Concomitant use to be taken into consideration:
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Others combinations:
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

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

Linked to Acerycal:

Concomitant use which requires special care:
Baclofen: Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

Concomitant use to be taken into consideration:
- Antihypertensive agents (such as beta-blockers) and vasodilatators:
  Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine. Concomitant use with nitroglycerine and other nitrates or other vasodilatators, may further reduce blood pressure and therefore should be considered with caution.
- Corticosteroids, tetracosactide: reduction in antihypertensive effect (salt and water retention due to corticosteroids).
- Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin): increased antihypertensive effect and increased risk of orthostatic hypotension.
- Amifostine: may potentiate the antihypertensive effect of amlodipine.
- Tricyclic antidepressants/antipsychotics/anaesthetics: increased antihypertensive effect and increased risk of orthostatic hypotension.

4.6 Fertility, pregnancy and lactation

Given the effects of the individual components in this combination product on pregnancy and lactation:
Acerycal is not recommended during the first trimester of pregnancy. Acerycal is contraindicated during the second and third trimesters of pregnancy.
Acerycal is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Acerycal 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 amlodipine
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses (see section 5.3).Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Lactation:
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
It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility :
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with perindopril or amlodipine given separately and ranked under the MedDRA classification by body system and under the following frequency:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**	
		Amlodipine	**Perindopril**
Blood and the lynphatic System Disorders	Leucopenia/neutropenia (see section 4.4)	Very rare	Very rare
	Agranulocytosis or pancytopenia (see section 4.4)	-	Very rare
	Thrombocytopenia (see section 4.4)	Very rare	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)	-	Very rare
	Decrease in haemoglobin and haematocrit	-	Very rare
Immune System Disorders	Allergic reactions	Very rare	Uncommon
Metabolism and Nutrition Disorders	Hyperglycaemia	Very rare	-
	Hypoglycaemia (see sections 4.4 and 4.5)	-	Not known
Psychiatric disorders	Insomnia	Uncommon	-
	Mood changes (including anxiety)	Uncommon	Uncommon
	Depression	Uncommon	-
	Sleep disturbances	-	Uncommon
	Confusion	Rare	Very rare

Nervous System disorders	Somnolence (especially at the beginning of the treatment)	Common	-
	Dizziness (especially at the beginning of the treatment)	Common	Common
	Headache (especially at the beginning of the treatment)	Common	Common
	Dysgeusia	Uncommon	Common
	Tremor	Uncommon	-
	Hypoesthaesia Paresthaesia	Uncommon Uncommon	- Common
	Syncope	Uncommon	-
	Hypertonia	Very rare	-
	Peripheral neuropathy	Very rare	-
	Vertigo	-	Common
Eye Disorders	Visual disturbances (including diplopia)	Uncommon	Common
Ear and labyrinth disorders	Tinnitus	Uncommon	Common
Cardiac Disorders	Palpitations	Common	-
	Angina pectoris	-	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see section 4.4)	Very rare	Very rare
	Arrythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Very rare	Very rare
Vascular Disorders	Flushing	Common	-
	Hypotension (and effects related to hypotension)	Uncommon	Common
	Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	-	Very rare
	Vasculitis	Very Rare	Not known
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	Uncommon	Common
	Rhinitis	Uncommon	Very rare
	Cough	Very rare	Common
	Bronchospasm	-	Uncommon
	Eosinophilic pneumonia	-	Very rare
Gastro-intestinal Disorders	Gingival hyperplasia	Very rare	-
	Abdominal pain, nausea	Common	Common
	Vomiting	Uncommon	Common
	Dyspepsia	Uncommon	Common
	Altered bowel habits	Uncommon	-
	Dry mouth	Uncommon	Uncommon
	Diarrhoea, constipation	Uncommon	Common
	Pancreatitis	Very rare	Very rare
	Gastritis	Very rare	-
Hepato-biliary Disorders	Hepatitis, jaundice Hepatitis either cytolitic or cholestatic (see section 4.4)	Very rare -	- Very rare
	Hepatic enzymes increased (mostly consistent with cholestasis)	Very rare	-
Skin and Subcutaneous Tissue Disorders	Quincke's oedema Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)	Very rare Very rare	- Uncommon

	Erythema multiform	Very rare	Very rare
	Alopecia	Uncommon	-
	Purpura	Uncommon	-
	Skin discoloration	Uncommon	-
	Hyperhidrosis	Uncommon	Uncommon
	Prurit	Uncommon	Common
	Rash, exanthema	Uncommon	Common
	Urticaria	Very rare	Uncommon
	Stevens-Johnson Syndrome	Very rare	-
	Exfoliative dermatitis	Very rare	-
	Photosensitivity	Very rare	-
Musculoskeletal And Connective Tissue Disorders	Ankle swelling	Common	-
	Arthralgia, myalgia	Uncommon	-
	Muscle cramps	Uncommon	Common
	Back pain	Uncommon	-
Renal and Urinary Disorders	Micturition disorder, nocturia, increased urinary frequency	Uncommon	-
	Renal impairment	-	Uncommon
	Acute renal failure	-	Very rare
Reproductive System and Breast Disorders	Impotence	Uncommon	Uncommon
	Gynaecomastia	Uncommon	-
General Disorders and Administration Site Condition	Oedema	Common	-
	Fatigue	Common	-
	Chest pain	Uncommon	-
	Asthenia	Uncommon	Common
	Pain	Uncommon	-
	Malaise	Uncommon	-
Investigations	Weight increase, weight decrease	Uncommon	-
	Serum bilirubin and liver enzymes elevation	-	Rare
	Increases in blood urea and serum creatinine, hyperkalaemia (see section 4.4)	-	Not known

Additional information linked to amlodipine

Exceptional cases of extrapyramidal syndrome have been reported.

4.9 Overdose

There is no information on overdosage with Acerycal in humans.
For amlodipine, experience with intentional overdose in humans is limited.
Symptoms: available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.
Treatment: clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and calcium channel blockers, ATC code: C09BB04

Perindopril:
Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity *in vitro*.

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.

Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years.
Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to 8 mg perindopril tertbutylamine (equivalent to 10 mg perindopril arginine) (n=6110) or placebo (n=6108).

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.

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

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. 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.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

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.

Patients with coronary artery disease (CAD):

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-center, randomized, double- blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Table 1. Incidence of significant clinical outcomes for CAMELOT					
Cardiovascular event rates, No. (%)				Amlodipine vs. placebo	
Outcomes	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value
Primary Endpoint Adverse cardiovascular events	- 110 (16.6)	- 151 (23.1)	- 136 (20.2)	- 0.69 (0.54-0.88)	- *.003*

Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.98)	.002
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.58 (0.41-	.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.82)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	0.73 (0.37-	.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	1.46)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	0.50 (0.19-	.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	1.32)	.24
				2.46 (0.48-	
				12.7)	
				0.59 (0.14-	
				2.47)	
				NA	
				2.6 (0.50-13.4)	

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.

Use in patients with heart failure:
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.
A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.
In a follow-up, long term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT):

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 allcause mortality between amlodipine-based therapy and chlorthalidone-based therapy, RR 0.96 (95% CI [0.89-1.02] p=0.20).

5.2 Pharmacokinetic properties

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

Perindopril:
After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.

Perindopril is a prodrug. Twenty seven percent 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.

The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steadystate within 4 days.

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure (see section 4.2). Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.

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).

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

The bioavailability of amlodipine is not affected by food intake.

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

Use in the elderly: the time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Use in patients with impaired hepatic function: Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

5.3 Preclinical safety data

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

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

Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in periand postnatal mortality have been observed.
No carcinogenicity has been observed in long term studies in rats and mice.

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/m2 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/m2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.
* Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470B)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container & outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

30 tablets in a plastic container equipped with a flow reducer and a stopper containing a desiccant gel, in an outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Limited
Unit L2, North Ring Business Park
Santry
Dublin 9

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1151/167/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27th January 2012

10 DATE OF REVISION OF THE TEXT

August 2013