

Public Assessment Report

Scientific discussion

**Perindopril/Indapamide STADA
2/0.625 mg, tablets
and
4/1,25 mg, tablets
(perindopril tert-butylamine)**

NL/H/4686/001-002/DC

Date: 6 March 2023

This module reflects the scientific discussion for the approval of Perindopril/Indapamide STADA 2/0.625 mg, tablets and 4/1,25 mg, tablets. The procedure was finalised in the United Kingdom (UK/H/4139/001-002). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Public Assessment Report

Decentralised Procedure

Perindopril/Indapamide 2mg/0.625 mg Tablets
Perindopril/Indapamide 4mg/1.25 mg Tablets

PL 25258/0022

PL 25258/0023

PL 25258/0065

PL 25258/0066

PL 25258/0067

PL 25258/0068

UK/H/2631/01-02/DC

UK/H/4139/01-02/DC

UK/H/4140/01-02/DC

Glenmark Generics (Europe) Ltd

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Glenmark Generics (Europe) Ltd Marketing Authorisations (licences) for the medicinal products Perindopril/Indapamide 2mg/0.625 mg and 4mg/1.25 mg Tablets (product licence numbers: PL 25258/0022-0023 and PL 25258/0065-0068) on 20 May 2011. These medicines are available on prescription only.

Perindopril and indapamide belong to a group of medicines known as the anti-hypertensive medicines, which means that they are used to treat high blood pressure. Perindopril belongs to class known as the ACE inhibitors; these work by widening the blood vessels, which makes it easier for the heart to pump blood through them. Indapamide belongs to a group of medicines called diuretics; these work by allowing kidneys to produce more urine than normal. Perindopril and indapamide work together to lower and control blood pressure.

The data submitted in support of these applications for Perindopril/Indapamide 2mg/0.625 mg and 4mg/1.25 mg Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Information about Decentralised Procedure

Name of the products in the Reference Member State	Perindopril/Indapamide 2mg/0.625 mg and 4mg/1.25 mg Tablets
Type of applications	Generic (Article 10.1)
Names of the active substances (INN)	Perindopril tert-butylamine and indapamide
Pharmacotherapeutic classification (ATC code)	ACE inhibitors and diuretics (C09BA04)
Pharmaceutical form and strengths	Tablets; 2mg/0.625mg and 4mg/1.25mg
Reference numbers for the Decentralised Procedure	UK/H/2631/01-02/DC UK/H/4139/01-02/DC UK/H/4140/01-02/DC
Reference Member State	UK
Member States concerned	UK/H/2631/01-02/DC: BE, DE, DK, EL, ES, FR, IE, IT, NL, PT UK/H/4139/01-02/DC: BE, BG, CZ, DE, ES, NL, SK UK/H/4140/01-02/DC: DE
Start of Decentralised Procedure	13 February 2009
End date of Decentralised Procedure	20 April 2011
Marketing Authorisation number	PL 25258/0022-0023 PL 25258/0065-0068
Name and address of the authorisation holder	Glenmark Generics (Europe) Ltd Laxmi House 2 B Draycott Avenue, Kenton, Middlesex HA3 0BU United Kingdom

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 2mg/0.625 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2mg/0.625mg Tablets

Each tablet contains 2 mg perindopril tert-butylamine salt, equivalent to 1.669 mg perindopril and 0.625mg indapamide.

Excipient: each tablet contains 58.47mg of lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

2mg/0.625mg: White, rod shaped tablets having 'P' and 'I' engraved on either side of score line on one side and score line on the other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Treatment of essential hypertension for patients whose blood pressure is not adequately controlled on perindopril alone.

4.2 Posology and method of administration

Route of administration: Oral use

It is recommended that one Perindopril/Indapamide 2mg/0.625mg Tablet is taken daily, preferably in the morning before a meal. The dose should be adjusted according to the patient profile and blood pressure response. If blood pressure is not adequately controlled the dose may be increased to one Perindopril/Indapamide 4mg/1.25mg Tablet daily.

When clinically appropriate, direct change from monotherapy with perindopril to Perindopril/Indapamide may be considered. Individual dose titration with the components may be required.

Elderly (See 4.4)

Treatment should be initiated at a dose of 2mg/0.625mg daily with consideration of the blood pressure response and renal function.

Patients with renal impairment (See 4.3 & 4.4)

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

In patients with moderate renal impairment (creatinine clearance 30 to 60ml/min), it is recommended to start treatment with the adequate dosage of the free combination. It is not necessary to change the dose when creatinine clearance is greater than or equal to 60ml/min. Usual medical follow-up will include frequent monitoring of creatinine and potassium levels.

Patients with hepatic impairment (See 4.3 & 4.4)

In severe hepatic impairment, treatment is contraindicated.

In patients with moderate hepatic impairment, no dose modification is required.

Children and adolescents

Perindopril/Indapamide is not recommended for use in children and adolescents as the safety and efficacy of perindopril in children and adolescents, alone or in combination has not been established.

4.3 Contraindications

The use of Perindopril/Indapamide is contraindicated in patients with:

- Hypersensitivity to perindopril, indapamide or any of the excipients.

Linked to Perindopril:

- Hypersensitivity to any other ACE inhibitors.
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy
- Hereditary/idiopathic angioedema
- Second and third trimesters of pregnancy (see section 4.6)

Linked to Indapamide:

- Hypersensitivity to any other sulphonamides
- Severe renal impairment (creatinine clearance below 30 ml/min)
- Hepatic encephalopathy
- Severe hepatic impairment
- Hypokalaemia
- As a general rule, this medicine is inadvisable in combination with non antiarrhythmic agents causing torsades de pointes (see section 4.5)
- Lactation (see section 4.6)

Due to the lack of sufficient therapeutic experience, Perindopril/Indapamide should not be used in:

- Dialysis patients
- Patients with untreated decompensated heart failure.

4.4 Special warnings and precautions for use

Special warnings

Common to perindopril and indapamide

Lithium:

The combination of lithium and the combination of perindopril and indapamide is usually not recommended (see section 4.5).

Linked to Perindopril:

Risk of Neutropenia/ Agranulocytosis in Immuno-suppressed patients:

The risk of neutropenia appears to be dose and type-related and is dependent on patient's clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus, scleroderma and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor.

Strict compliance with the predetermined dose seems to be the best way to prevent the onset of these events.

However, if an angiotensin converting enzyme inhibitor is to be administered to this type of patient, the risk/benefit ratio should be evaluated carefully.

Angioedema (Quincke's oedema)

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. In such cases, treatment with perindopril should be stopped immediately and the patient should be monitored until the oedema has disappeared. 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. Involvement of the tongue, glottis or larynx may lead to an obstruction of the airways. A subcutaneous injection of adrenaline at 1:1000 (0.3 ml to 0.5 ml) should be administered quickly and other appropriate measures taken.

The prescription of an angiotensin converting enzyme inhibitor should not subsequently be considered in these patients (see section 4.3).

Patients with a previous history of Quincke's oedema which was not linked to taking an angiotensin converting enzyme inhibitor have an increased risk of Quincke's oedema with an angiotensin converting enzyme inhibitor.

Anaphylactic reactions during desensitisation

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

Haemodialysis patients: Anaphylactoid reactions during membrane exposure

There have been reports of patients experiencing sustained life-threatening anaphylactoid reactions while receiving ACE inhibitors during dialysis with high flux membranes or low density lipoprotein apheresis with dextran sulphate adsorption. ACE inhibitors should be avoided in such patients. However these reactions could be prevented by temporary withdrawal of ACE inhibitors for at least 24 hours before treatment in patients who require both ACE inhibitors and LDL apheresis.

Potassium-sparing diuretics, potassium salts:

The combination of perindopril and potassium-sparing diuretics, potassium salts is usually not recommended (see section 4.5).

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 anti-hypertensive 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).

Linked to Indapamide:

When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause hepatic encephalopathy. Administration of the diuretic-containing product, should be stopped immediately if this occurs.

Sultopride:

The combination of indapamide and sultopride is usually not recommended (see section 4.5).

Special precautions for use

Linked to Perindopril/Indapamide

Renal impairment

In cases of severe renal impairment (creatinine clearance < 30 ml/min), treatment is contraindicated.

In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only. In these patients usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.

The drug is usually not recommended in case of bilateral renal artery stenosis or a single functioning kidney.

Hypotension and water and electrolyte depletion:

There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhoea or vomiting.

Regular monitoring of plasma electrolytes should be carried out in such patients.

Marked hypotension may require the implementation of an intravenous infusion of isotonic saline.

Transient hypotension is not a contraindication to continuation of treatment. After re-establishment of a satisfactory blood volume and blood pressure, treatment can be started again either at a reduced dose or with only one of the constituents.

Potassium levels:

The combination of perindopril and indapamide does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. As with any antihypertensive agent in combination with a diuretic, regular monitoring of plasma potassium levels should be carried out.

Excipients:

This product contains lactose monohydrate. Patients with rare hereditary conditions such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

Linked to Perindopril:

Cough

A dry cough has been reported with the use of ACE inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If the prescription of an angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be considered.

Children:

The efficacy and tolerability of perindopril in children and adolescents, alone or in a combination, have not been established.

Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion).

Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium-free diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascities.

The blocking of this system with an angiotensin converting enzyme inhibitor may therefore cause, particularly at the time of the first administration and

during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, although rare, and with a variable time to onset. In such cases, the treatment should then be initiated at a lower dose and increased progressively.

Elderly:

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

Patients with known atherosclerosis:

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

Renovascular hypertension

The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.

If Perindopril/Indapamide is prescribed to patients with known or suspected renal artery stenosis, treatment should be started in a hospital setting at a low dose and renal function and potassium levels should be monitored, since some patients have developed a functional renal insufficiency which was reversed when treatment was stopped.

Other populations at risk:

In patients with severe cardiac insufficiency (grade IV) or in patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose. Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped: the ACE inhibitor should be added to the beta-blocker.

Anaemia:

Anaemia has been observed in patients who have had a kidney transplant or have been undergoing dialysis. The reduction in haemoglobin levels is more apparent as initial values were high. This effect does not seem to be dose-dependent but may be linked to the mechanism of action of angiotensin converting enzyme inhibitors.

This reduction in haemoglobin is slight, occurs within 1 to 6 months, and then remains stable. It is reversible when treatment is stopped. Treatment can be continued with regular haematological testing.

Surgery

Angiotensin converting enzyme inhibitors can cause hypotension in cases of anaesthesia, especially when the anaesthetic administered is an agent with hypotensive potential.

It is therefore recommended that treatment with long-acting angiotensin converting enzyme inhibitors such as perindopril should be discontinued where possible one day before surgery.

Aortic stenosis / hypertrophic cardiomyopathy

ACE inhibitors should be used with caution in patients with an obstruction in the outflow of the left ventricle

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).

Hyperkalaemia:

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended. The drug is usually not recommended in case of raised plasma levels of potassium.

Linked to Indapamide:

Water and electrolyte balance:

Sodium levels:

These should be tested before treatment is started, then at regular intervals. All diuretic treatment can cause a reduction in sodium levels, which may have serious consequences. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients (see sections 4.8 and 4.9).

Potassium levels:

Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. The risk of onset of lowered potassium levels (<3.4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure.

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

Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe rhythm disorders, in particular torsades de pointes, which may be fatal.

In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment.

If low potassium levels are detected, correction is required.

Calcium levels: Thiazide diuretics and thiazide-related diuretics may reduce urinary excretion of calcium and cause a mild and transient increase in plasma calcium levels. Markedly raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases the treatment should be stopped before investigating the parathyroid function.

Blood glucose: Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

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

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

In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient, according to the Cockcroft formula:

$$clcr = (140 - \text{age}) \times \text{body weight} / 0.814 \times \text{plasma creatinine level}$$

with: age expressed in years

body weight in kg

plasma creatinine level in micromol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0.85.

Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.

Athletes:

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

4.5 Interaction with other medicinal products and other forms of interaction

Linked to Perindopril/Indapamide

Combinations which are not recommended:

Lithium

reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of perindopril combined with indapamide with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Combinations which require special care:

Baclofen

Concomitant treatment of anti-hypertensives with baclofen is likely to cause increased hypotension; the dosage of Perindopril/Indapamide should be adjusted accordingly and close monitoring of blood pressure and renal function is recommended.

Non-steroidal anti-inflammatory medicinal products (including acetylsalicylic acid at high doses): the administration of a non-steroidal anti-inflammatory medicinal product may reduce the diuretic, natriuretic and antihypertensive effects in some patients. In elderly patients and patients who may be dehydrated there is a risk of acute renal failure, therefore monitoring of renal function at the initiation of treatment is recommended. Patients should be well hydrated.

Combinations, which require some care:

Imipramine-like antidepressants (tricyclics), neuroleptics

Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Corticosteroids, tetracosactide

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

Other antihypertensive agents: use of other antihypertensive medicinal products with perindopril/indapamide could result in additional blood pressure lowering effect.

Linked to Perindopril:

Combinations which are not recommended:

Potassium-sparing diuretics (spironolactone, triamterene, alone or in combination), potassium salts

ACE inhibitors attenuate diuretic induced potassium loss. Potassium-sparing diuretics e.g. spironolactone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium (potentially lethal). If concomitant use is indicated because of documented hypokalaemia they should be used with caution and with frequent monitoring of serum potassium and by ECG.

Combinations which require special care:

Antidiabetic agents (insulin, hypoglycaemic sulphonamides): Reported with captopril and enalapril.

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 (improvement in glucose tolerance with a resulting reduction in insulin requirements).

Combinations which require some care:

Anaesthetic drugs

ACE inhibitors may enhance the hypotensive effects of certain anaesthetic drugs. Therefore the combination of perindopril/indapamide should be avoided during this time.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide

Concomitant administration with ACE inhibitors may lead to an increased risk of leucopenia.

Diuretics (thiazide or loop diuretics): Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypotension when initiating therapy with perindopril.

Linked to Indapamide:

Combinations which are not recommended:

Sultopride: Increased risk of ventricular arrhythmia, especially torsades de pointes (hypokalaemia favours the occurrence of this adverse event) (see section 4.4).

Combinations which require special care:

Torsades de pointes inducing drugs : Due to the risk of hypokalaemia, indapamide should be administered with caution when associated with medicinal products that induced torsades de pointes such as class IA antiarrhythmic agents (quinidine, hydroquinidine, disopyramide); class III antiarrhythmic agents (amiodarone, dofetilide, ibutilide, bretylium, sotalol); some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of low potassium levels and correction if necessary : monitoring of the QT interval.

Potassium-lowering drugs: amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), Tetracosactide, stimulant laxatives
Increased risk of low potassium levels (additive effect).

Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides. Non-stimulant laxatives should be used.

Cardiac Glycosides

Low potassium levels favour the toxic effects of cardiac glycosides.

Potassium levels and electrocardiogram should be monitored and treatment reconsidered if necessary.

Combinations, which require some care:

Metformin

Metformin can cause possible renal impairment which in effect can lead to lactic acidosis. Linked to diuretics and in particular to loop diuretics.

Do not use Metformin when plasma creatinine levels exceed 15mg/l (135micromol/l) in men and 12mg/l (100micromol/l) in women.

Iodinated contrast media

In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.

Calcium (salts)

Risk of increased levels of calcium due to reduced elimination of calcium in the urine.

Ciclosporin

Risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no salt and water depletion.

4.6 Pregnancy and lactation

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).

Pregnancy

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 fetotoxicity (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).

As indapamide is a chlorosulphamoyl diuretic its administration to pregnant women must be avoided. Diuretics should never be given as treatment for physiological oedema of pregnancy (which does therefore not require treatment). Exposure to thiazide diuretics during the third trimester can lead to reduction of maternal plasma volume and uteroplacental blood flow, which may cause feto-placental ischemia, with a risk of impaired fetal growth.

Moreover, rare cases of hypoglycemia and thrombocytopenia in neonates have been reported following exposure near term.

Lactation

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

Indapamide is contraindicated during lactation. Indapamide is excreted in human milk. Thiazide diuretics have been associated, during breast-feeding, with decrease or even suppression of lactation. Hypersensitivity to sulfonamide-derived drugs, hypokalaemia and nuclear icterus might occur. As serious adverse reactions might occur in breastfed infants, a decision should be made whether to discontinue breastfeeding or to discontinue therapy taking account the importance of this therapy for the mother.

4.7 Effects on ability to drive and use machines

Perindopril/Indapamide has minor or moderate influence on the ability to drive and use machines. Neither of the two active substances affect alertness but individual reactions related to low blood pressure may occur in some patients, particularly at the start of the treatment or in combination with another antihypertensive medication. As a result, the ability to drive or operate machines may be impaired.

4.8 Undesirable effects

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide. Approximately four percent of the patients on treatment with Perindopril/Indapamide may experience hypokalaemia (potassium level < 3.4 mmol/l).

The following undesirable effects have been observed during treatment with perindopril/indapamide and ranked under the following frequency:

Very common ($>1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1000$ to $<1/100$); rare ($\geq 1/10000$ to $<1/1000$); very rare ($<1/10000$); not known (cannot be estimated from the available data).

Vascular disorders

Uncommon: Hypotension whether orthostatic or not.

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, Leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia,

Anaemia (see section 4.4) has been reported with angiotensin converting enzyme inhibitors in specific circumstances (patients who have had kidney transplants, patients undergoing haemodialysis).

Nervous system disorders

Uncommon: Headache, asthenia, feelings of dizziness, mood disturbance and/or sleep disturbances, paresthesia.

Respiratory, thoracic and mediastinal disorders

Common: Dry cough has been reported with the use of angiotensin converting enzyme inhibitors.

Gastrointestinal disorders

Common: Constipation, dry mouth, nausea, epigastric pain, anorexia, abdominal pains, taste disturbance

Very rare: Pancreatitis, in the case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy (see sections 4.3 and 4.4)

Skin and subcutaneous tissue disorders

Uncommon: Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic asthmatic reactions.

Maculopapular eruptions, purpura, possible aggravation of pre-existing acute disseminated lupus erythematosus.

Skin rash

Very rare:

Angioedema (Quincke's oedema) (see section 4.4)

Musculoskeletal and connective tissue disorders

Uncommon: Cramps.

Investigations:

- Potassium depletion with particularly serious reduction in levels of potassium in some at risk populations (see section 4.4).
 - Reduced sodium levels with hypovolaemia causing dehydration and orthostatic hypotension.
 - Increase in uric acid levels and in blood glucose levels during treatment.
 - Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped. This increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.
 - Increased levels of potassium, usually transitory.
- Rare (> 1/10,000, < 1/1,000):
- raised plasma calcium levels.

4.9 Overdose

The most common adverse event in the case of an overdose is hypotension.

This can be linked to the following:

Nausea, vomiting, cramps, sleepiness, mental confusion, oliguria which could progress to anuria (due to hypovolaemia), electrolyte imbalance (low sodium and potassium levels)

The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal.

If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an IV infusion of isotonic saline may be given, or any other method of volaemic expansion may be used. Perindoprilat, the active form of perindopril, can be dialysed (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor and Diuretic

ATC code: C09BA04

Perindopril/Indapamide is a combination of perindopril tert-butylamine salt and indapamide to treat essential hypertension in patients whose blood pressure is not adequately controlled by perindopril alone. Perindopril tert-butylamine salt is an angiotensin converting enzyme inhibitor. Indapamide is a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.

Pharmacological mechanism of action

Perindopril/Indapamide produces an added synergy of the antihypertensive effects of the two components.

Linked to Perindopril

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

This results in:

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

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

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

Perindopril reduces the work of the heart:

- By a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins: reduction in pre-load
 - By reduction of the total peripheral resistance: reduction in afterload.
- Studies carried out on patients with cardiac insufficiency have shown:
- A reduction in left and right ventricular filling pressures,
 - A reduction in total peripheral vascular resistance,
 - An increase in cardiac output and an improvement in the cardiac index,
 - An increase in regional blood flow in muscle.

Exercise test results also showed improvement.

Linked to Indapamide

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the re-absorption of sodium in the cortical dilution segment. It increases urine output and in effect increases excretion of sodium and chloride and to a lesser extent, the excretion of potassium and magnesium, so having an antihypertensive action.

Characteristics of Antihypertensive action

Linked to Perindopril/Indapamide

In hypertensive patients regardless of age, Perindopril/Indapamide exert a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing. This antihypertensive effect lasts for 24 hours. The reduction in blood pressure is obtained in less than one month without tachyphylaxis; stopping treatment has no rebound effect. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the products administered alone.

Linked to Perindopril

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

The antihypertensive activity after a single dose is at its maximum between 4 and 6 hours and remains consistent during the course of 24 hours.

At 24 hours, there is a high degree of residual blocking of angiotensin converting enzyme (80%)

In patients who respond well to treatment, blood pressure is stabilised after one month without any signs of tachyphylaxis.

Withdrawal of treatment has no rebound effect on hypertension.

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

If necessary, the addition of a thiazide diuretic leads to an additive synergy. The combination of an angiotensin converting enzyme inhibitor with a thiazide diuretic decreases the hypokalaemia risk associated with the diuretic alone.

Linked to Indapamide

Indapamide, as monotherapy, has an antihypertensive effect, which lasts for 24 hours, this effect occurs at doses at which the diuretic properties are minimal. Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance.

Indapamide reduces left ventricular hypertrophy.

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

Furthermore, it has been shown that regardless of the duration of treatment in hypertensive patients, indapamide:

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

5.2 Pharmacokinetic properties

Linked to Perindopril/Indapamide

There is no significant difference between the pharmacokinetic characteristics of perindopril and indapamide co-administered and those obtained from perindopril and indapamide administered separately.

Linked to 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 steady-state within 4 days. 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).

Indapamide

Absorption

Indapamide is absorbed from the digestive tract rapidly and completely.

The peak plasma level reached in humans is approximately one hour after oral administration of the product. Plasma protein binding is 79%.

Elimination

The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70% of the dose) and faeces (22%) in the form of inactive metabolites.

Special population

Renal insufficiency:

The pharmacokinetics of patients with renal failure is unaffected.

5.3 Preclinical safety data

Perindopril and indapamide in combination has slightly increased toxicity than that of its components.

Renal manifestations do not seem to be potentiated in rats. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seem to be increased in the rat (compared to perindopril alone).

Nonetheless, these adverse effects are shown at dose levels giving a very marked safety margin in comparison to the therapeutic doses used.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica hydrophobic colloidal Cellulose, microcrystalline

Lactose monohydrate

Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

2 months after first opening the laminated pouch containing the blister strip of tablets

6.4 Special precautions for storage

Store in the original package to protect from moisture.

When unopened, this medicinal product does not require any special temperature storage conditions.

Once the laminated pouch is opened, blister strips should be stored in the outer box below 30°C

6.5 Nature and contents of container

The tablets are packed in PVC / PVdC – Aluminium blisters within a protective aluminium pouch, including a desiccant protecting the tablets from moisture. The desiccant should not be swallowed.

Pack Sizes

30, 90 and 100

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0022

PL 25258/0065

PL 25258/0067

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/05/2011

10 DATE OF REVISION OF THE TEXT

20/05/2011

1 NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 4mg/1.25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

4mg/1.25mg Tablets

Each tablet contains 4 mg perindopril tert-butylamine salt, equivalent to 3.338 mg perindopril and 1.25mg indapamide

Excipient: each tablet contains 58.47 mg of lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

4mg/1.25mg: White, rod shaped tablets having 'PI' debossed on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Treatment of essential hypertension for patients whose blood pressure is not adequately controlled on perindopril alone.

4.2 Posology and method of administration

Route of administration: Oral use

It is recommended that one Perindopril/Indapamide 2mg/0.625mg Tablet is taken daily, preferably in the morning before a meal. The dose should be adjusted according to the patient profile and blood pressure response. If blood pressure is not adequately controlled the dose may be increased to one Perindopril/Indapamide 4mg/1.25mg Tablet daily.

When clinically appropriate, direct change from monotherapy with perindopril to Perindopril/Indapamide may be considered. Individual dose titration with the components may be required.

Elderly (See 4.4)

Treatment should be initiated at a dose of 2mg/0.625mg daily with consideration of the blood pressure response and renal function.

Patients with renal impairment (See 4.3 & 4.4)

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

In patients with moderate renal impairment (creatinine clearance 30 to 60ml/min), it is recommended to start treatment with the adequate dosage of

the free combination. It is not necessary to change the dose when creatinine clearance is greater than or equal to 60ml/min. Usual medical follow-up will include frequent monitoring of creatinine and potassium levels.

Patients with hepatic impairment (See 4.3 & 4.4)

In severe hepatic impairment, treatment is contraindicated.

In patients with moderate hepatic impairment, no dose modification is required.

Children and adolescents

Perindopril/Indapamide is not recommended for use in children and adolescents as the safety and efficacy of perindopril in children and adolescents, alone or in combination has not been established.

4.3 Contraindications

The use of Perindopril/Indapamide is contraindicated in patients with:

- Hypersensitivity to perindopril, indapamide or any of the excipients.

Linked to Perindopril:

- Hypersensitivity to any other ACE inhibitors.
- History of angioedema (Quincke's oedema) associated with previous ACE inhibitor therapy
- Hereditary/idiopathic angioedema
- Second and third trimesters of pregnancy (see section 4.6)

Linked to Indapamide:

- Hypersensitivity to any other sulphonamides
- Severe renal impairment (creatinine clearance below 30 ml/min)
- Hepatic encephalopathy
- Severe hepatic impairment
- Hypokalaemia
- As a general rule, this medicine is inadvisable in combination with non antiarrhythmic agents causing torsades de pointes (see section 4.5)
- Lactation (see section 4.6)

Due to the lack of sufficient therapeutic experience, Perindopril/Indapamide should not be used in:

- Dialysis patients
- Patients with untreated decompensated heart failure.

4.4 Special warnings and precautions for use

Special warnings

Common to perindopril and indapamide

Lithium:

The combination of lithium and the combination of perindopril and indapamide is usually not recommended (see section 4.5).

Linked to Perindopril:

Risk of Neutropenia/ Agranulocytosis in Immuno-suppressed patients:

The risk of neutropenia appears to be dose and type-related and is dependent on patient's clinical status. It is rarely seen in uncomplicated patients but may occur in patients with some degree of renal impairment especially when it is associated with collagen vascular disease e.g. systemic lupus erythematosus, scleroderma and therapy with immunosuppressive agents. It is reversible after discontinuation of the ACE inhibitor.

Strict compliance with the predetermined dose seems to be the best way to prevent the onset of these events.

However, if an angiotensin converting enzyme inhibitor is to be administered to this type of patient, the risk/benefit ratio should be evaluated carefully.

Angioedema (Quincke's oedema)

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. In such cases, treatment with perindopril should be stopped immediately and the patient should be monitored until the oedema has disappeared. 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. Involvement of the tongue, glottis or larynx may lead to an obstruction of the airways. A subcutaneous injection of adrenaline at 1:1000 (0.3 ml to 0.5 ml) should be administered quickly and other appropriate measures taken.

The prescription of an angiotensin converting enzyme inhibitor should not subsequently be considered in these patients (see section 4.3).

Patients with a previous history of Quincke's oedema which was not linked to taking an angiotensin converting enzyme inhibitor have an increased risk of Quincke's oedema with an angiotensin converting enzyme inhibitor.

Anaphylactic reactions during desensitisation

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

Haemodialysis patients: Anaphylactoid reactions during membrane exposure

There have been reports of patients experiencing sustained life-threatening anaphylactoid reactions while receiving ACE inhibitors during dialysis with high flux membranes or low density lipoprotein apheresis with dextran sulphate adsorption. ACE inhibitors should be avoided in such patients.

However these reactions could be prevented by temporary withdrawal of ACE inhibitors for at least 24 hours before treatment in patients who require both ACE inhibitors and LDL apheresis.

Potassium-sparing diuretics, potassium salts:

The combination of perindopril and potassium-sparing diuretics, potassium salts is usually not recommended (see section 4.5).

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 anti-hypertensive 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).

Linked to Indapamide:

When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause hepatic encephalopathy. Administration of the diuretic-containing product, should be stopped immediately if this occurs.

Sultopride:

The combination of indapamide and sultopride is usually not recommended (see section 4.5).

Special precautions for use

Linked to Perindopril/Indapamide

Renal impairment

In cases of severe renal impairment (creatinine clearance < 30 ml/min), treatment is contraindicated.

In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only. In these patients usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.

The drug is usually not recommended in case of bilateral renal artery stenosis or a single functioning kidney.

Hypotension and water and electrolyte depletion:

There is a risk of sudden hypotension in the presence of pre-existing sodium depletion (in particular in individuals with renal artery stenosis). Therefore systematic testing should be carried out for clinical signs of water and electrolyte depletion, which may occur with an intercurrent episode of diarrhoea or vomiting.

Regular monitoring of plasma electrolytes should be carried out in such patients.

Marked hypotension may require the implementation of an intravenous infusion of isotonic saline.

Transient hypotension is not a contraindication to continuation of treatment. After re-establishment of a satisfactory blood volume and blood pressure, treatment can be started again either at a reduced dose or with only one of the constituents.

Potassium levels:

The combination of perindopril and indapamide does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure. As with any antihypertensive agent in combination with a diuretic, regular monitoring of plasma potassium levels should be carried out.

Excipients:

This product contains lactose monohydrate. Patients with rare hereditary conditions such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

Linked to Perindopril:

Cough

A dry cough has been reported with the use of ACE inhibitors. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If the prescription of an angiotensin converting enzyme inhibitor is still preferred, continuation of treatment may be considered.

Children:

The efficacy and tolerability of perindopril in children and adolescents, alone or in a combination, have not been established.

Risk of arterial hypotension and/or renal insufficiency (in cases of cardiac insufficiency, water and electrolyte depletion).

Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium-free diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascities.

The blocking of this system with an angiotensin converting enzyme inhibitor may therefore cause, particularly at the time of the first administration and during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, although rare, and with a variable time to onset.

In such cases, the treatment should then be initiated at a lower dose and increased progressively.

Elderly:

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

Patients with known atherosclerosis:

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

Renovascular hypertension

The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.

If Perindopril/Indapamide is prescribed to patients with known or suspected renal artery stenosis, treatment should be started in a hospital setting at a low dose and renal function and potassium levels should be monitored, since some patients have developed a functional renal insufficiency which was reversed when treatment was stopped.

Other populations at risk:

In patients with severe cardiac insufficiency (grade IV) or in patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment should be started under medical supervision with a reduced initial dose. Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped: the ACE inhibitor should be added to the beta-blocker.

Anaemia:

Anaemia has been observed in patients who have had a kidney transplant or have been undergoing dialysis. The reduction in haemoglobin levels is more apparent as initial values were high. This effect does not seem to be dose-dependent but may be linked to the mechanism of action of angiotensin converting enzyme inhibitors.

This reduction in haemoglobin is slight, occurs within 1 to 6 months, and then remains stable. It is reversible when treatment is stopped. Treatment can be continued with regular haematological testing.

Surgery

Angiotensin converting enzyme inhibitors can cause hypotension in cases of anaesthesia, especially when the anaesthetic administered is an agent with hypotensive potential.

It is therefore recommended that treatment with long-acting angiotensin converting enzyme inhibitors such as perindopril should be discontinued where possible one day before surgery.

Aortic stenosis / hypertrophic cardiomyopathy

ACE inhibitors should be used with caution in patients with an obstruction in the outflow of the left ventricle

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).

Hyperkalaemia:

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended. The drug is usually not recommended in case of raised plasma levels of potassium.

Linked to Indapamide:

Water and electrolyte balance:

Sodium levels:

These should be tested before treatment is started, then at regular intervals. All diuretic treatment can cause a reduction in sodium levels, which may have serious consequences. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients (see sections 4.8 and 4.9).

Potassium levels:

Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. The risk of onset of lowered potassium levels (<3.4 mmol/l) should be prevented in some high risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure.

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

Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe rhythm disorders, in particular torsades de pointes, which may be fatal.

In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment.

If low potassium levels are detected, correction is required.

Calcium levels: Thiazide diuretics and thiazide-related diuretics may reduce urinary excretion of calcium and cause a mild and transient increase in plasma calcium levels. Markedly raised levels of calcium may be related to undiagnosed hyperparathyroidism. In such cases the treatment should be stopped before investigating the parathyroid function.

Blood glucose: Monitoring of blood glucose is important in diabetic patients, particularly when potassium levels are low.

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

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

In the elderly the value of plasma creatinine levels should be adjusted to take account of the age, weight and sex of the patient, according to the Cockcroft formula:

$$clcr = (140 - \text{age}) \times \text{body weight} / 0.814 \times \text{plasma creatinine level}$$

with: age expressed in years

body weight in kg

plasma creatinine level in micromol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0.85.

Hypovolaemia, resulting from the loss of water and sodium caused by the diuretic at the start of treatment, causes a reduction in glomerular filtration. It may result in an increase in blood urea and creatinine levels. This transitory functional renal insufficiency is of no adverse consequence in patients with normal renal function but may however worsen a pre-existing renal impairment.

Athletes:

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

4.5 Interaction with other medicinal products and other forms of interaction

Linked to Perindopril/Indapamide

Combinations which are not recommended:

Lithium

reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may further increase lithium levels and enhance the risk of lithium toxicity with ACE inhibitors. Use of perindopril combined with indapamide with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Combinations which require special care:

Baclofen

Concomitant treatment of anti-hypertensives with baclofen is likely to cause increased hypotension; the dosage of Perindopril/Indapamideshould be adjusted accordingly and close monitoring of blood pressure and renal function is recommended.

Non-steroidal anti-inflammatory medicinal products (including acetylsalicylic acid at high doses) : the administration of a non-steroidal anti-inflammatory medicinal product may reduce the diuretic, natriuretic and antihypertensive effects in some patients. In elderly patients and patients who may be dehydrated there is a risk of acute renal failure, therefore monitoring of renal function at the initiation of treatment is recommended. Patients should be well hydrated.

Combinations, which require some care:

Imipramine-like antidepressants (tricyclics), neuroleptics

Increased antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

Corticosteroids, tetracosactide

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

Other antihypertensive agents : use of other antihypertensive medicinal products with perindopril/indapamide could result in additional blood pressure lowering effect.

Linked to Perindopril:**Combinations which are not recommended:**

Potassium-sparing diuretics (spironolactone, triamterene, alone or in combination), potassium salts

ACE inhibitors attenuate diuretic induced potassium loss. Potassium-sparing diuretics e.g. spironolactone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium (potentially lethal). If concomitant use is indicated because of documented hypokalaemia they should be used with caution and with frequent monitoring of serum potassium and by ECG.

Combinations which require special care:

Antidiabetic agents (insulin, hypoglycaemic sulphonamides): Reported with captopril and enalapril.

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 (improvement in glucose tolerance with a resulting reduction in insulin requirements).

Combinations which require some care:

Anaesthetic drugs

ACE inhibitors may enhance the hypotensive effects of certain anaesthetic drugs. Therefore the combination of perindopril/indapamide should be avoided during this time.

Allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procainamide

Concomitant administration with ACE inhibitors may lead to an increased risk of leucopenia.

Diuretics (thiazide or loop diuretics): Prior treatment with high dose diuretics may result in volume depletion and in a risk of hypotension when initiating therapy with perindopril.

Linked to Indapamide:

Combinations which are not recommended:

Sultopride: Increased risk of ventricular arrhythmia, especially torsades de pointes (hypokalaemia favours the occurrence of this adverse event) (see section 4.4).

Combinations which require special care:

Torsades de pointes inducing drugs : Due to the risk of hypokalaemia, indapamide should be administered with caution when associated with medicinal products that induced torsades de pointes such as class IA antiarrhythmic agents (quinidine, hydroquinidine, disopyramide); class III antiarrhythmic agents (amiodarone, dofetilide, ibutilide, bretylium, sotalol); some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenones (droperidol, haloperidol), other neuroleptics (pimozide); other substances such as bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, IV vincamine, methadone, astemizole, terfenadine. Prevention of low potassium levels and correction if necessary: monitoring of the QT interval.

Potassium-lowering drugs: amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), Tetracosactide, stimulant laxatives
Increased risk of low potassium levels (additive effect).

Monitoring of potassium levels, and correction if necessary; particular consideration required in cases of treatment with cardiac glycosides. Non-stimulant laxatives should be used.

Cardiac Glycosides

Low potassium levels favour the toxic effects of cardiac glycosides.

Potassium levels and electrocardiogram should be monitored and treatment reconsidered if necessary.

Combinations, which require some care:

Metformin

Metformin can cause possible renal impairment which in effect can lead to lactic acidosis. Linked to diuretics and in particular to loop diuretics. Do not use Metformin when plasma creatinine levels exceed 15mg/l (135micromol/l) in men and 12mg/l (100micromol/l) in women.

Iodinated contrast media

In cases of dehydration caused by diuretics, there is an increased risk of acute renal insufficiency, particularly when high doses of iodinated contrast media are used. Rehydration should be carried out before the iodinated compound is administered.

Calcium (salts)

Risk of increased levels of calcium due to reduced elimination of calcium in the urine.

Ciclosporin

Risk of increased creatinine levels with no change in circulating levels of ciclosporin, even when there is no salt and water depletion.

4.6 Pregnancy and lactation

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).

Pregnancy

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 fetotoxicity (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).

As indapamide is a chlorosulphamoyl diuretic its administration to pregnant women must be avoided. Diuretics should never be given as treatment for physiological oedema of pregnancy (which does therefore not require treatment). Exposure to thiazide diuretics during the third trimester can lead to reduction of maternal plasma volume and uteroplacental blood flow, which may cause feto-placental ischemia, with a risk of impaired fetal growth.

Moreover, rare cases of hypoglycemia and thrombocytopenia in neonates have been reported following exposure near term.

Lactation

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

Indapamide is contraindicated during lactation. Indapamide is excreted in human milk. Thiazide diuretics have been associated, during breast-feeding, with decrease or even suppression of lactation. Hypersensitivity to sulfonamide-derived drugs, hypokalaemia and nuclear icterus might occur. As serious adverse reactions might occur in breastfed infants, a decision should be made whether to discontinue breastfeeding or to discontinue therapy taking account the importance of this therapy for the mother.

4.7 Effects on ability to drive and use machines

Perindopril/Indapamide has minor or moderate influence on the ability to drive and use machines. Neither of the two active substances affect alertness but individual reactions related to low blood pressure may occur in some patients, particularly at the start of the treatment or in combination with another antihypertensive medication. As a result, the ability to drive or operate machines may be impaired.

4.8 Undesirable effects

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide. Approximately four percent of the patients on treatment with Perindopril/Indapamide may experience hypokalaemia (potassium level < 3.4 mmol/l).

The following undesirable effects have been observed during treatment with perindopril/indapamide and ranked under the following frequency:

Very common ($>1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1000$ to $<1/100$); rare ($\geq 1/10000$ to $<1/1000$); very rare ($<1/10000$); not known (cannot be estimated from the available data).

Vascular disorders

Uncommon: Hypotension whether orthostatic or not.

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, Leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia,

Anaemia (see section 4.4) has been reported with angiotensin converting enzyme inhibitors in specific circumstances (patients who have had kidney transplants, patients undergoing haemodialysis).

Nervous system disorders

Uncommon: Headache, asthenia, feelings of dizziness, mood disturbance and/or sleep disturbances, paresthesia.

Respiratory, thoracic and mediastinal disorders

Common: Dry cough has been reported with the use of angiotensin converting enzyme inhibitors.

Gastrointestinal disorders

Common: Constipation, dry mouth, nausea, epigastric pain, anorexia, abdominal pains, taste disturbance

Very rare: Pancreatitis, in the case of hepatic insufficiency, there is a possibility of onset of hepatic encephalopathy. (see sections 4.3 and 4.4)

Skin and subcutaneous tissue disorders

Uncommon: Hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic asthmatic reactions.

Maculopapular eruptions, purpura, possible aggravation of pre-existing acute disseminated lupus erythematosus.

Skin rash

Very rare:

Angioedema (Quincke's oedema) (see section 4.4)

Musculoskeletal and connective tissue disorders

Uncommon: Cramps.

Investigations:

- Potassium depletion with particularly serious reduction in levels of potassium in some at risk populations (see section 4.4).
 - Reduced sodium levels with hypovolaemia causing dehydration and orthostatic hypotension.
 - Increase in uric acid levels and in blood glucose levels during treatment.
 - Slight increase in urea and in plasma creatinine levels, reversible when treatment is stopped. This increase is more frequent in cases of renal artery stenosis, arterial hypertension treated with diuretics, renal insufficiency.
 - Increased levels of potassium, usually transitory.
- Rare (> 1/10,000, < 1/1,000):
- raised plasma calcium levels.

4.9 Overdose

The most common adverse event in the case of an overdose is hypotension.

This can be linked to the following:

Nausea, vomiting, cramps, sleepiness, mental confusion, oliguria which could progress to anuria (due to hypovolaemia), electrolyte imbalance (low sodium and potassium levels)

The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal.

If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary an IV infusion of isotonic saline may be given, or any other method of volaemic expansion may be used. Perindoprilat, the active form of perindopril, can be dialysed (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitor and Diuretic
ATC code: C09BA04

Perindopril/Indapamide is a combination of perindopril tert-butylamine salt and indapamide to treat essential hypertension in patients whose blood pressure is not adequately controlled by perindopril alone. Perindopril tert-butylamine salt is an angiotensin converting enzyme inhibitor. Indapamide is a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.

Pharmacological mechanism of action

Perindopril/Indapamide produces an added synergy of the antihypertensive effects of the two components.

Linked to Perindopril

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

This results in:

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

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

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

Perindopril reduces the work of the heart:

- By a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins: reduction in pre-load
 - By reduction of the total peripheral resistance: reduction in afterload.
- Studies carried out on patients with cardiac insufficiency have shown:
- A reduction in left and right ventricular filling pressures,
 - A reduction in total peripheral vascular resistance,
 - An increase in cardiac output and an improvement in the cardiac index,
 - An increase in regional blood flow in muscle.
- Exercise test results also showed improvement.

Linked to Indapamide

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the re-absorption of sodium in the cortical dilution segment. It increases urine output and in effect increases excretion of sodium and chloride and to a lesser extent, the excretion of potassium and magnesium, so having an antihypertensive action.

Characteristics of Antihypertensive action

Linked to Perindopril/Indapamide

In hypertensive patients regardless of age, Perindopril/Indapamide exert a dose-dependent antihypertensive effect on diastolic and systolic arterial pressure whilst supine or standing. This antihypertensive effect lasts for 24 hours. The reduction in blood pressure is obtained in less than one month without tachyphylaxis; stopping treatment has no rebound effect. During clinical trials, the concomitant administration of perindopril and indapamide produced antihypertensive effects of a synergic nature in relation to each of the products administered alone.

Linked to Perindopril

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

The antihypertensive activity after a single dose is at its maximum between 4 and 6 hours and remains consistent during the course of 24 hours. At 24 hours, there is a high degree of residual blocking of angiotensin converting enzyme (80%)

In patients who respond well to treatment, blood pressure is stabilised after one month without any signs of tachyphylaxis.

Withdrawal of treatment has no rebound effect on hypertension.

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

If necessary, the addition of a thiazide diuretic leads to an additive synergy. The combination of an angiotensin converting enzyme inhibitor with a thiazide diuretic decreases the hypokalaemia risk associated with the diuretic alone.

Linked to Indapamide

Indapamide, as monotherapy, has an antihypertensive effect, which lasts for 24 hours, this effect occurs at doses at which the diuretic properties are minimal. Its antihypertensive action is proportional to an improvement in arterial compliance and a reduction in total and arteriolar peripheral vascular resistance.

Indapamide reduces left ventricular hypertrophy.

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

Furthermore, it has been shown that regardless of the duration of treatment in hypertensive patients, indapamide:

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

5.2 Pharmacokinetic properties

Linked to Perindopril/Indapamide

There is no significant difference between the pharmacokinetic characteristics of perindopril and indapamide co-administered and those obtained from perindopril and indapamide administered separately.

Linked to 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 steady-state within 4 days. 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).

Indapamide

Absorption

Indapamide is absorbed from the digestive tract rapidly and completely.

The peak plasma level reached in humans is approximately one hour after oral administration of the product. Plasma protein binding is 79%.

Elimination

The elimination half-life is between 14 and 24 hours (average 18 hours). Repeated administration does not produce accumulation. Elimination is mainly in the urine (70% of the dose) and faeces (22%) in the form of inactive metabolites.

Special population

Renal insufficiency:

The pharmacokinetics of patients with renal failure is unaffected.

5.3 Preclinical safety data

Perindopril and indapamide in combination has slightly increased toxicity than that of its components.

Renal manifestations do not seem to be potentiated in rats. However, the combination produces gastro-intestinal toxicity in the dog and the toxic effects on the mother seem to be increased in the rat (compared to perindopril alone).

Nonetheless, these adverse effects are shown at dose levels giving a very marked safety margin in comparison to the therapeutic doses used. Preclinical studies performed separately with perindopril and indapamide did not show genotoxic, carcinogenic or teratogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica hydrophobic colloidal Cellulose, microcrystalline
Lactose monohydrate
Magnesium Stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

2 months after first opening the laminated pouch containing the blister strip of tablets

6.4 Special precautions for storage

Store in the original package to protect from moisture.

When unopened, this medicinal product does not require any special temperature storage conditions.

Once the laminated pouch is opened, blister strips should be stored in the outer box below 30°C

6.5 Nature and contents of container

The tablets are packed in PVC / PVdC – Aluminium blisters within a protective aluminium pouch, including a desiccant protecting the tablets from moisture. The desiccant should not be swallowed.

Pack Sizes

30, 90 and 100

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Limited
Laxmi House, 2 B Draycott Avenue,
Kenton, Middlesex HA3 0BU,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0023

PL 25258/0066

PL 25258/0068

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/05/2011

10 DATE OF REVISION OF THE TEXT

20/05/2011

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Perindopril/Indapamide 2 mg/0.625 mg Tablets Perindopril/Indapamide 4 mg/1.25 mg Tablets

Perindopril tert-butylamine 2 mg / Indapamide 0.625 mg
Perindopril tert-butylamine 4 mg / Indapamide 1.25 mg

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Perindopril/Indapamide Tablets is and what it is used for
2. Before you take Perindopril/Indapamide Tablets
3. How to take Perindopril/Indapamide Tablets
4. Possible side effects
5. How to store Perindopril/Indapamide Tablets
6. Further information

1. WHAT PERINDOPRIL/INDAPAMIDE TABLETS IS AND WHAT IT IS USED FOR

Perindopril/Indapamide Tablets is a combination of Perindopril and Indapamide. They belong to a group of anti-hypertensive medicines, which are used in the treatment of high blood pressure.

Perindopril belongs to a class of ACE inhibitors. These work by widening the blood vessels in your body, which make it easier for your heart to pump blood around through them.

Indapamide belongs to a group of medicines called diuretics. These work by allowing your kidneys to produce more urine than normal.

Each of the individual medicines work together to lower your blood pressure and control it.

2. BEFORE YOU TAKE PERINDOPRIL/INDAPAMIDE TABLETS

Do not take Perindopril/Indapamide Tablets

- If you are allergic (hypersensitive) to Perindopril or Indapamide or any of the other ingredients of Perindopril/Indapamide Tablets.
- If you are allergic to any other ACE inhibitors or diuretics (Sulphonamides).
- If you have experienced swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing, with previous ACE inhibitor therapy. This is a condition called angioneurotic oedema (Quincke's oedema). Alternatively, if you or any of your family members have had these symptoms tell your doctor as soon as possible.
- If you have heart problems or are on medication (See "Taking other medicines")
- If you are more than 3 months pregnant. It is also better to avoid Perindopril/Indapamide Tablets in early pregnancy – see pregnancy section.
- If you are breastfeeding
- If you have kidney failure or are receiving dialysis
- If you have serious liver disease or suffer from a condition called hepatic encephalopathy (which is brain and nervous system impairment caused by severe liver disease)
- If your doctor has told you, that you have low or high blood potassium.

Take special care with Perindopril/Indapamide Tablets

Tell your doctor before you start to take this medicine:

- If you have bilateral renal artery stenosis (narrowing of the main blood vessel leading to the kidney) or a single functioning kidney
- If you have diabetes
- If you are on a low salt diet or use salt substitutes, which contain potassium
- If you take lithium or potassium-sparing diuretics (e.g. Spironolactone, Triamterene)
- If you are taking a medicine which is a combination with a potassium-sparing diuretic
- If you are going to have an operation under general anaesthetic, as you may need to stop treatment a few days beforehand.
- If you have Atherosclerosis (a disease of the arteries in which blood vessel walls thicken and harden due to cholesterol deposit)
- If you are to undergo LDL apheresis (which is removal of cholesterol from your blood by a machine).
- If you are going to have desensitisation treatment to reduce the effects of an allergy (e.g. bee or wasp sting)
- If you are to undergo a medical test that requires injection of a substance that makes organs like the kidney or stomach visible on an x-ray (iodinated contrast agent)
- If you have anaemia (a condition when the red blood cells in your body carry less oxygen, some of the symptoms of anaemia include tiredness, headaches, dizziness)
- If you have Gout (a disease where uric acid crystals cause swollen joints)

- If you have a collagen disease such as systemic lupus erythematosus or scleroderma.
- You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Perindopril/Indapamide Tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead. Perindopril/Indapamide Tablets is not recommended in early pregnancy, and must not be taken when you are more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should avoid Perindopril/Indapamide Tablets with:

- Lithium
- Potassium-sparing diuretics (e.g. spironolactone, triamterene alone or in combination) potassium salts
- Allopurinol (treatment of gout)
- Procainamide (treatment of irregular heartbeat)
- Systemic corticosteroids (used to treat various conditions including severe asthma and rheumatoid arthritis)
- Other medicines to treat high blood pressure
- immunosuppressants used for the treatment of autoimmune disorders or following transplant surgery to prevent rejection (e.g. Ciclosporin)

Treatment with Perindopril/Indapamide Tablets can be affected by other medicines. Tell your doctor if you are taking any of the following medicines as special care may be required:

- Astemizole or Terfenadine (antihistamines for hayfever or allergies)
- Bepridil (used to treat angina pectoris - an uncomfortable feeling in this chest)
- Erythromycin by injection, Moxifloxacin, Sparfloxacin (antibiotics)
- Halofantrine (used to treat certain types of malaria)
- Pentamidine (used to treat pneumonia which is a serious lung infection)
- Vincamine (used to treat disorders of the brain in elderly)
- Baclofen (to treat muscle stiffness occurring in diseases such as multiple sclerosis)
- Medicines to treat diabetes such as insulin, Metformin or hypoglycaemic sulphonamides
- Non-Steroidal anti-inflammatory drugs (e.g. Ibuprofen) or high dose salicylates (e.g. Aspirin)
- Potassium lowering drugs e.g. Amphotericin B (by injection, to treat severe fungal disease), glucocorticoids and mineralocorticoids (systemic route), or stimulant laxatives (e.g. Senna)
- Potassium-sparing diuretics (amiloride, spironolactone, triamterene)
- Thiazide or loop diuretics
- Medicines to treat irregular heart beat such as Quinidine, Hydroquinidine, Disopyramide, Amiodarone, Bretylium, Dofetilide, Ibutilide and Sotalol.
- Medicines to treat mental disorders such as depression, anxiety, schizophrenia (e.g. tricyclic antidepressants, neuroleptics such as Chlorpromazine, Cyamemazine, Levomepromazine, Thioridazine, Trifluoperazine, Amisulpride, Tiapride, Droperidol, Haloperidol, Pimozide)
- Cisapride, Dipheganil, Mizolastine
- Methadone
- Sultopride (used in the treatment of psychotic disorders)
- Tetracosactide (used to treat Crohn's disease)
- calcium salts

Taking Perindopril/Indapamide Tablets with food and drink

It is recommended that Perindopril/Indapamide Tablets are taken in the morning on an empty stomach. Swallow the tablets with a glass of water.

Pregnancy and breast-feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking Perindopril/Indapamide Tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead. Perindopril/Indapamide Tablets is not recommended in early pregnancy, and must not be taken when you are more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breastfeeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. Perindopril/Indapamide Tablets should not be taken by mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

Perindopril/Indapamide Tablets has minor or moderate influence on the ability to drive and use machines. This medicine does not affect alertness but reactions related to low blood pressure may occur in some patients. This can cause dizziness or weakness. If affected your ability to drive or operate machinery may be impaired therefore caution is advised.

Important information about some of the ingredients of Perindopril/Indapamide Tablets

Perindopril/Indapamide Tablets contains a small amount of lactose. If you have been told by your doctor that you have an intolerance to some sugars, (Rare hereditary problems, galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption) you should contact your doctor before taking the medicine.

3. HOW TO TAKE PERINDOPRIL/INDAPAMIDE TABLETS

Always take Perindopril/Indapamide Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The dose may be increased depending on your condition and other medicines you are taking. Take Perindopril/Indapamide Tablets your medicine by mouth only.

The usual dose is:

High Blood pressure:

It is recommended that one Perindopril/Indapamide 2mg/0.625mg tablet is taken in the morning before breakfast. If your blood pressure is not controlled then your doctor may increase your dose to one Perindopril/Indapamide 4mg/1.25mg tablet daily.

In older people with high blood pressure:

It is recommended that one Perindopril/Indapamide 2mg/0.625mg tablet is taken in the morning before breakfast.

If you take more Perindopril/Indapamide Tablets than you should

If you take more Perindopril/Indapamide Tablets than you should or someone else has taken your medicine contact your doctor or pharmacist immediately. The most common effect of an overdose is low blood pressure, the symptoms of this can be dizziness, sleepiness or nausea. It may help lying down with your legs raised up into the air.

If you forget to take Perindopril/Indapamide Tablets

Take your tablet as soon as you remember unless it is time for your next dose. Take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Perindopril/Indapamide Tablets

If you stop taking Perindopril/Indapamide Tablets tell your doctor as soon as possible. Normally the treatment for high blood pressure is long term.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines Perindopril/Indapamide Tablets can cause side effects, although not everybody gets them. These can include:

Common: affects 1 to 10 users in 100

- Dry cough
- Dry mouth
- Constipation
- Nausea (feeling sick)
- Stomach pain or discomfort
- Loss of appetite
- Taste loss
- Low levels of potassium

Uncommon: affects 1 to 10 users in 1,000

- Low blood pressure
- Headache
- Feeling light headed when standing up
- Feelings of dizziness
- Mood swings
- Sleep disturbance
- Hypersensitivity reaction (allergic reaction)
- Cramps
- Paresthesia (numbness or pins and needles on your hands or feet)

Rare: affects 1 to 10 users in 10,000

- Raised levels of calcium in the blood

Very rare: affects less than 1 user in 10,000

- Thrombocytopenia: Low blood platelet count. Symptoms may include bleeding or bruising more easily than normal.
- Leucopenia or Agranulocytosis: lack of white blood cells. Symptoms may include frequent infections such as fever, severe chills, sore throat or mouth ulcers
- Aplastic anaemia: a rare type of anaemia in which there is a reduction in your red blood cells, white blood cells and platelets
- Haemolytic anaemia: illness resulting from the destruction of red blood cells
- Anaemia in patients following a kidney transplant or on haemodialysis
- Pancreatitis: inflammation of the pancreas in case of hepatic failure
- Hepatic encephalopathy: brain and nervous system damage related to complicated liver disease

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If you have any blood tests, tell the doctor that you are taking Perindopril/Indapamide Tablets since the following may be seen:

Low or high levels of potassium

Low levels of sodium

High levels of uric acid and glucose

Slightly high levels of urea and creatinine.

5. HOW TO STORE PERINDOPRIL/INDAPAMIDE TABLETS

Keep out of the reach and sight of children.

Store in the original package to protect from moisture.

When unopened, this medicinal product does not require any special temperature storage conditions.

Once the laminated pouch is opened, blister strips should be stored in the outer box below 30°C

Any remaining tablets should be discarded two months after opening the pouch.

Do not use Perindopril/Indapamide Tablets after the expiry date which is stated on the label, blister, pouch and carton after EXP. The expiry date refers to the last day of the month. Medicines should not be disposed of via wastewater or household waste.

Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Perindopril/Indapamide Tablets contains

- The active substances are Perindopril tert-butylamine and Indapamide
- Each tablet contains 2mg Perindopril tert-butylamine equivalent to 1.669mg perindopril and 0.625mg Indapamide
- Each tablet contains 4mg Perindopril tert-butylamine equivalent to 3.338mg perindopril and 1.25mg Indapamide
- The other ingredients are:
 - Lactose Monohydrate
 - Magnesium stearate
 - Silica, hydrophobic colloidal
 - Cellulose, Microcrystalline

What Perindopril/Indapamide Tablets looks like and contents of the pack

Perindopril/Indapamide 2mg/0.625mg Tablet

White, rod shaped tablets engraved with 'P' and 'I' on either side of the break-line on one side and a break-line on the other side. The tablet can be broken into equal halves.

Perindopril/Indapamide 4mg/1.25mg Tablet

White rod shaped tablets having 'PI' debossed on one side and plain on the other.

The tablets are packed in PVC / PVdC – Aluminium blisters within a protective aluminium pouch, including a desiccant protecting the tablets from moisture. The desiccant should not be swallowed.

Pack Sizes

30, 90 and 100

*Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Glenmark Generics (Europe) Limited
Laxmi House, 2B Drycote Avenue,
Kenton, Middlesex HA3 0BU,
United Kingdom

Manufacturer (s)

Glenmark Pharmaceuticals S.R.O.
Hvězdova 1716/2b, 140 78 Praha 4,
Czech Republic

Glenmark Generics (Europe) Limited
The Old Sawmill, Hatfield Park,
Hatfield, Hertfordshire, AL9 5PG
United Kingdom

This medicinal product is authorised in the Member States of the EEA under the following names:

Belgium	Perindopril/Indapamide Glenmark 2/0.625mg and 4/1.25mg Tabletten
Denmark	Perindopril tert-butylamin/Indapamid Glenmark
France	Perindopril/Indapamide Glenmark Generics 2mg/0.625mg comprimés/cable Perindopril/Indapamide Glenmark Generics 4mg/1.25mg comprimé
Germany	Perindopril/Indapamid Glenmark 2mg/0.625mg and 4mg/1.25mg Tabletten
Greece	Perindopril/Indapamide Glenmark
Ireland	Perindopril tert-butylamine/Indapamide Glenmark 2mg/0.625mg and 4mg/1.25mg Tablets
Italy	Perindopril/Indapamide EG 2/0.625mg and 4/1.25mg
The Netherlands	Perindopril tert-butylamine /Indapamide Glenmark 2/0.625mg and 4/1.25mg Tabletten
Portugal	Perindopril/Indapamide Glenmark 2/0.625mg and 4/1.25mg Comprimidos
Spain	Perindopril/Indapamide Glenmark Generics 2/0.625mg and 4/1.25mg comprimidos

This leaflet was last approved in 05/2011.

XXXXXXXXXX

Module 4

Labelling

PL 25258/0022:

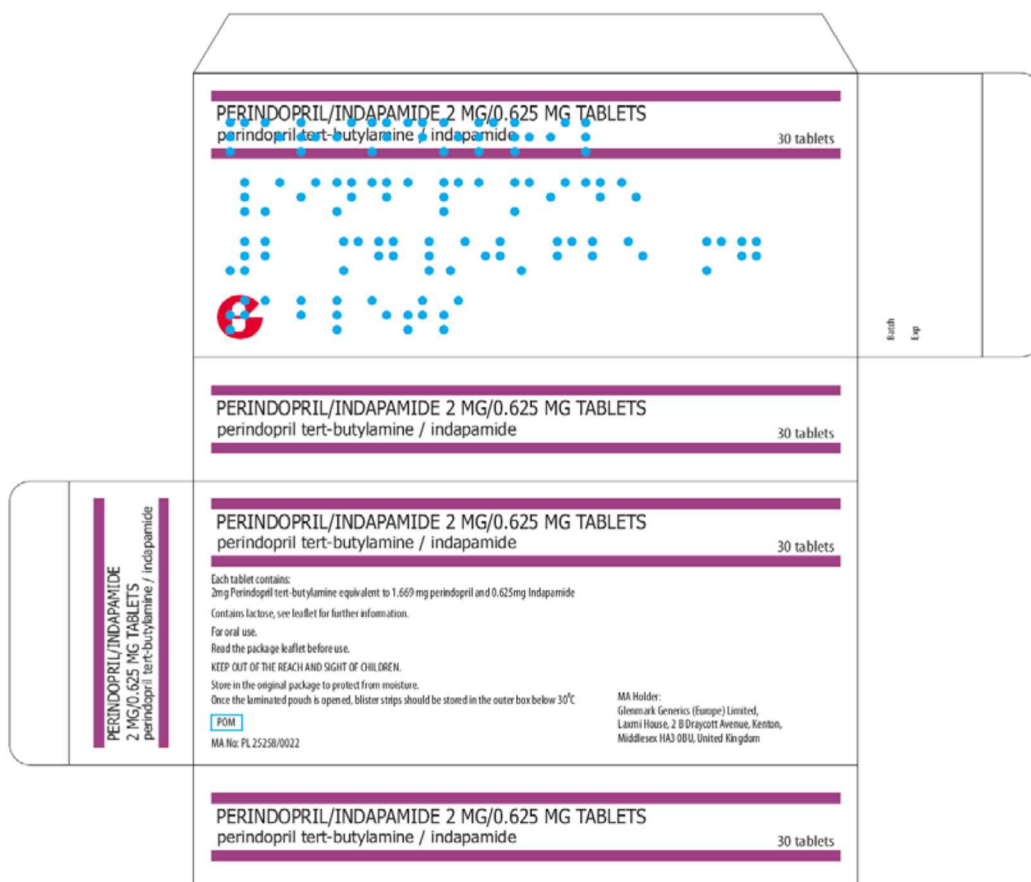
Pouch



Blister

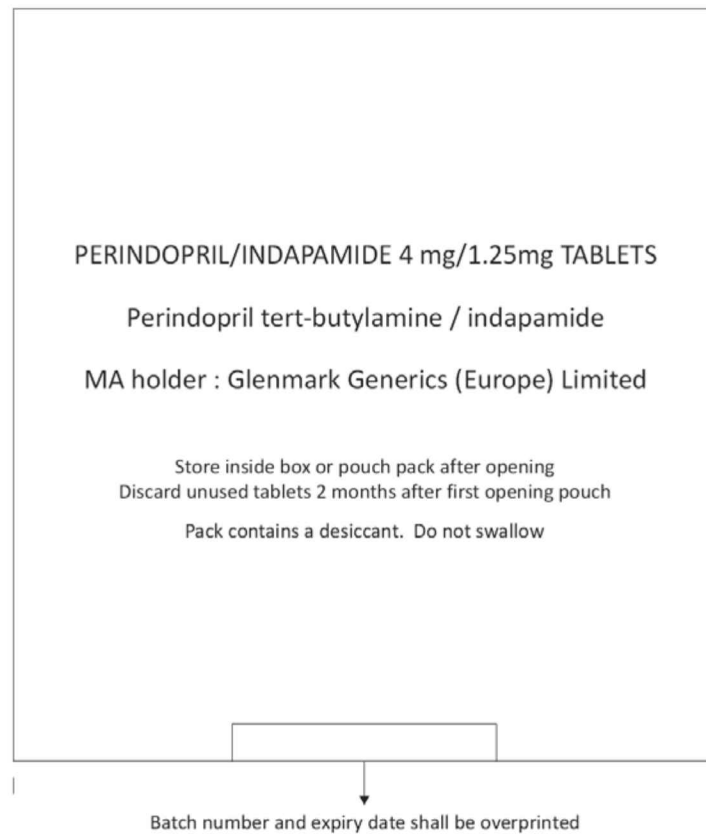


Carton



PL 25258/0023:

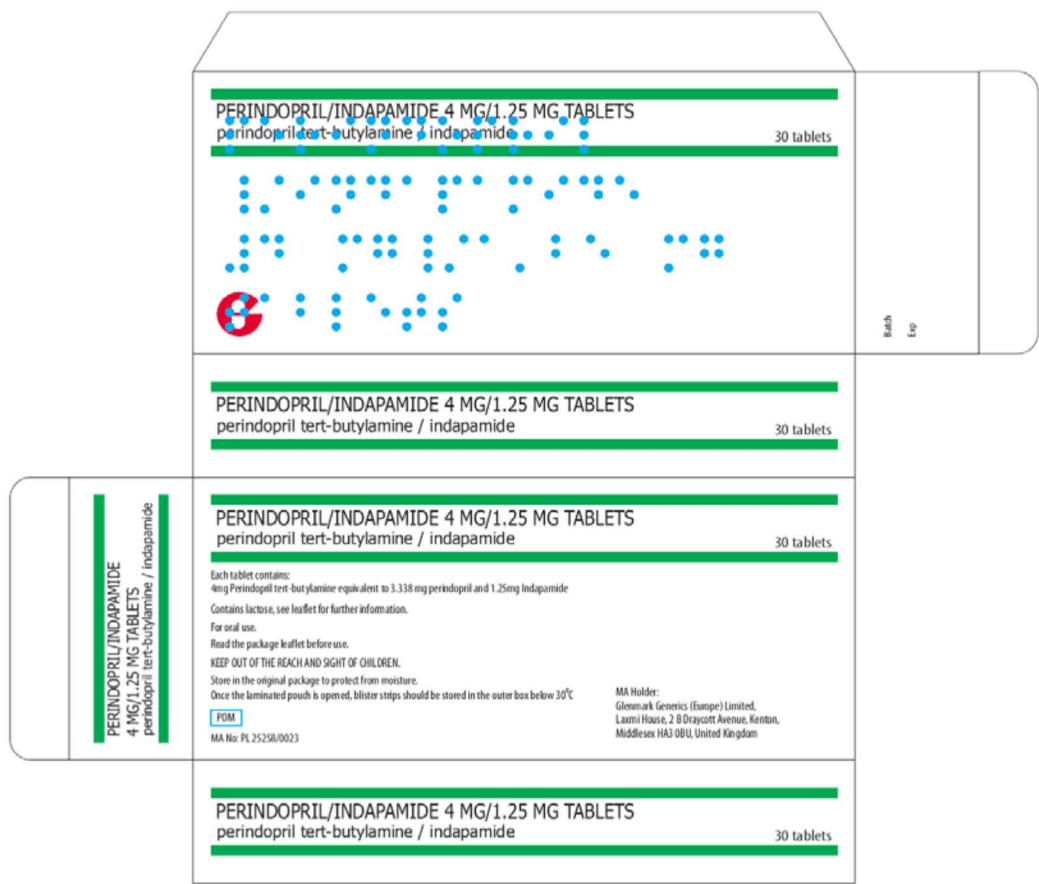
Pouch



Blister



Carton



The following label texts are the approved label texts for PL 25258/0065-0068. No label mock-ups have been provided. In accordance with medicines legislation, the products will not be marketed in the UK until approval of the label mock-ups has been obtained.

PL 25258/0065:

PARTICULARS TO APPEAR ON CARTON

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 2 mg/0.625 mg Tablets
perindopril tert-butylamine / indapamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains:
2mg Perindopril tert-butylamine equivalent to 1.669 mg perindopril and 0.625mg Indapamide

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: mm/yyyy

9. SPECIAL STORAGE CONDITIONS

Store in the original package to protect from moisture. Once the laminated pouch is opened, blister strips should be stored in the outer box below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 25258/0065

13. BATCH NUMBER

Batch: XXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Perindopril/Indapamide 2 mg/0.625 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**Blisters :****1. NAME OF THE MEDICINAL PRODUCT**

Perindopril/Indapamide 2 mg/0.625 mg Tablets
Perindopril tert-butylamine / indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

3. EXPIRY DATE

EXP: mm/yyyy

4. BATCH NUMBER

Batch : XXXX

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS / laminated pouch

Laminated Aluminium pouch :

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 2 mg/0.625 mg Tablets
Perindopril tert-butylamine / indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

3. SPECIAL STORAGE CONDITIONS

Store inside box or pouch pack after opening
Discard unused tablets 2 months after first opening pouch

4. EXPIRY DATE

EXP: mm/yyyy

5. BATCH NUMBER

Batch : XXXX

6. OTHER

Pack contains a desiccant. Do not swallow

PL 25258/0066:

PARTICULARS TO APPEAR ON CARTON

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 4 mg/1.25 mg Tablets
perindopril tert-butylamine / indapamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains:
4mg Perindopril tert-butylamine equivalent to 3.338 mg perindopril and 1.25mg Indapamide

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: mm/yyyy

9. SPECIAL STORAGE CONDITIONS

Store in the original package to protect from moisture. Once the laminated pouch is opened, blister strips should be stored in the outer box below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 25258/0066

13. BATCH NUMBER

Batch: XXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16 INFORMATION IN BRAILLE**

Perindopril/Indapamide 4 mg/1.25 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**Blisters :****1. NAME OF THE MEDICINAL PRODUCT**

Perindopril/Indapamide 4 mg/1.25 mg Tablets
Perindopril tert-butylamine / indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

3. EXPIRY DATE

EXP: mm/yyyy

4. BATCH NUMBER

Batch : XXXX

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS / laminated pouch

Laminated Aluminium pouch :

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 4 mg/1.25 mg Tablets
Perindopril tert-butylamine / indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

3. SPECIAL STORAGE CONDITIONS

Store inside box or pouch pack after opening
Discard unused tablets 2 months after first opening pouch

4. EXPIRY DATE

EXP: mm/yyyy

5. BATCH NUMBER

Batch : XXXX

6. OTHER

Pack contains a desiccant. Do not swallow

PL 25258/0067:

PARTICULARS TO APPEAR ON CARTON

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 2 mg/0.625 mg Tablets
perindopril tert-butylamine / indapamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains:
2mg Perindopril tert-butylamine equivalent to 1.669 mg perindopril and 0.625mg Indapamide

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: mm/yyyy

9. SPECIAL STORAGE CONDITIONS

Store in the original package to protect from moisture. Once the laminated pouch is opened, blister strips should be stored in the outer box below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 25258/0067

13. BATCH NUMBER

Batch: XXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16 INFORMATION IN BRAILLE**

Perindopril/Indapamide 2 mg/0.625 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**Blisters :****1. NAME OF THE MEDICINAL PRODUCT**

Perindopril/Indapamide 2 mg/0.625 mg Tablets
Perindopril tert-butylamine / indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

3. EXPIRY DATE

EXP: mm/yyyy

4. BATCH NUMBER

Batch : XXXX

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS / laminated pouch

Laminated Aluminium pouch :

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 2 mg/0.625 mg Tablets
Perindopril tert-butylamine / indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

3. SPECIAL STORAGE CONDITIONS

Store inside box or pouch pack after opening
Discard unused tablets 2 months after first opening pouch

4. EXPIRY DATE

EXP: mm/yyyy

5. BATCH NUMBER

Batch : XXXX

6. OTHER

Pack contains a desiccant. Do not swallow

PL 25258/0068:

PARTICULARS TO APPEAR ON CARTON

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 4 mg/1.25 mg Tablets
perindopril tert-butylamine / indapamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains:
4mg Perindopril tert-butylamine equivalent to 3.338 mg perindopril and 1.25mg Indapamide

3. LIST OF EXCIPIENTS

Contains lactose, see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: mm/yyyy

9. SPECIAL STORAGE CONDITIONS

Store in the original package to protect from moisture. Once the laminated pouch is opened, blister strips should be stored in the outer box below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 25258/0068

13. BATCH NUMBER

Batch: XXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Perindopril/Indapamide 4 mg/1.25 mg Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**Blisters :****1. NAME OF THE MEDICINAL PRODUCT**

Perindopril/Indapamide 4 mg/1.25 mg Tablets
Perindopril tert-butylamine / indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

3. EXPIRY DATE

EXP: mm/yyyy

4. BATCH NUMBER

Batch : XXXX

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS / laminated pouch

Laminated Aluminium pouch :

1. NAME OF THE MEDICINAL PRODUCT

Perindopril/Indapamide 4 mg/1.25 mg Tablets
Perindopril tert-butylamine / indapamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glenmark Generics (Europe) Ltd Laxmi House
2 B Draycott Avenue, Kenton,
Middlesex HA3 0BU
United Kingdom

3. SPECIAL STORAGE CONDITIONS

Store inside box or pouch pack after opening
Discard unused tablets 2 months after first opening pouch

4. EXPIRY DATE

EXP: mm/yyyy

5. BATCH NUMBER

Batch : XXXX

6. OTHER

Pack contains a desiccant. Do not swallow

Module 5

Scientific Discussion

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for Perindopril/Indapamide 2mg/0.625 mg and 4mg/1.25 mg Tablets in the treatment of essential hypertension for patients whose blood pressure is not adequately controlled on perindopril alone could be approved.

EXECUTIVE SUMMARY

Problem statement

These Decentralised applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that the proposed products are generic versions of the products Preterax 2mg/0.625mg Tablets and BiPreterax 4/1.25mg Tablets by Les Laboratoires Servier, registered since 25 November 1997. As these reference products have been authorised in the EU for more than 10 years, the legal basis of these applications is acceptable.

With the UK as the Reference Member State in these Decentralised Procedures, Glenmark Generics (Europe) Ltd applied for Marketing Authorisations for Perindopril/Indapamide 2mg/0.625 mg and 4mg/1.25 mg Tablets in the following CMS through the procedures indicated:

UK/H/2631/01-02/DC: BE, DE, DK, EL, ES, FR, IE, IT, NL, PT

UK/H/4139/01-02/DC: BE, BG, CZ, DE, ES, NL, SK

UK/H/4140/01-02/DC: DE

About the product

Hypertension is an important and established risk factor for cardiovascular disease. If treated effectively the risk of stroke can be reduced by approximately 35-40% and the risk of coronary heart disease by approximately 20-25%. Both perindopril and indapamide have been used in the treatment of hypertension and their safety profile is well known.

Perindopril belongs to class of compound called the ACE inhibitors. It is indicated for the treatment of hypertension, symptomatic heart failure, stable coronary artery disease and for the reduction of cardiac events in patients with myocardial infarction and/or revascularisation. Indapamide is a thiazide-related diuretic, primarily used for the treatment of high blood pressure. The action and uses of indapamide are similar to those of a thiazide diuretic. Indapamide tablets are approved for the treatment of hypertension either alone or in combination with other antihypertensives.

General comments on the submitted dossier

The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossiers regarding the quality, preclinical and clinical parts have been submitted.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GLP

No new preclinical studies were submitted in support of these applications, and none are needed for applications of this type.

GCP

Statements have been provided confirming that the submitted bioequivalence study was conducted in compliance with Good Clinical Practices (GCP), as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substances

(1) Perindopril tert-butylamine

Nomenclature

International non-proprietary name:

Perindopril Erbumine

European Pharmacopoeia name:

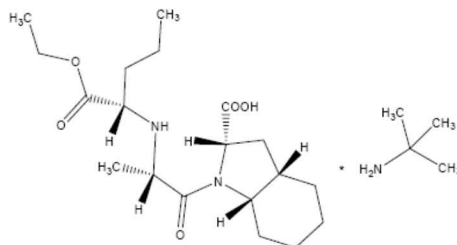
Perindopril tert-butylamine

Chemical name:

2-Methylpropan-2-amine (2S,3aS,7aS)-1-[(2S)-2-[[[(1S)-1 (ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate.

CAS number:

107133-36-8

Structure:**Molecular formula:**C₂₃H₄₃N₃O₅**Molecular mass:**

441.6

General Properties

White or almost white, crystalline powder, slightly hygroscopic. Freely soluble in water and in ethanol (96 per cent), sparingly soluble in methylene chloride (from Ph Eur)

Perindopril tert-butylamine is a well-known active substance described in the Ph Eur. All aspects of the manufacture and control of this drug substance are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of this drug substance for inclusion in this medicinal product.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the proposed packaging.

(2) IndapamideNomenclature**International non-proprietary name:**

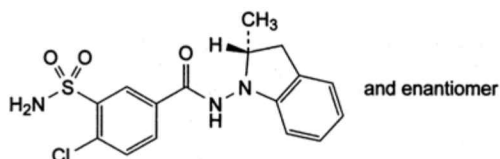
Indapamide

Chemical name:

4-Chloro-N-(2-methylindolin-1-yl)-3-sulphamoylbenzamide

CAS number:

26807-65-8

Structure:**Molecular formula:**C₁₆H₁₆ClN₃O₃S**Molecular weight:**

365.8

General properties

A white or almost white powder, practically insoluble in water, soluble in ethanol.

Indapamide is a well-known active substance described in the Ph Eur. All aspects of the manufacture and control of this drug substance are supported by an EDQM

Certificate of Suitability. This certificate is accepted as confirmation of the suitability of this drug substance for inclusion in this medicinal product.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the proposed packaging.

Drug product

The 2mg/0.625mg tablets are white, rod shaped tablets with 'P' and 'I' debossed on either side of score line on one side and a score line on the other side. The tablet can be divided into equal halves. Each tablet contains 2 mg perindopril tert-butylamine salt (equivalent to 1.669 mg perindopril) and 0.625mg indapamide.

The 4mg/1.25mg tablets are white, rod shaped tablets with 'PI' debossed on one side and are plain on the other side. Each tablet contains 4 mg perindopril tert-butylamine salt, (equivalent to 3.338 mg perindopril) and 1.25mg indapamide.

Both tablets also contain the pharmaceutical excipients silica hydrophobic colloidal, cellulose microcrystalline, lactose monohydrate and magnesium stearate. These excipients comply with current Ph Eur monograph requirements. Suitable declarations issued by the suppliers of the excipients to confirm compliance with the requirements of the relevant guideline and Directives with regard to TSE are also provided.

Pharmaceutical development

The objective of the development programme was to develop a formulation similar to the innovator products, Preterax 2 mg/0.625 mg Tablets and BiPreterax 4 mg/1.25 mg Tablets. A satisfactory account of the pharmaceutical development has been provided.

Manufacturing process

A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished product specification

The finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-closure system

The tablets are packed in PVC/PVdC/aluminium blisters within a protective aluminium pouch, including a desiccant protecting the tablets from moisture. The tablets are may come in packs of 30, 90 or 100 tablets, although not all pack sizes may be marketed.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

Stability of the product

Stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for this product, with an in use shelf life 2 months after first opening the laminated pouch containing the blister strip of tablets. The storage precautions 'Store in the original package to protect from moisture', 'When unopened, this medicinal product does not require any special temperature storage conditions' and 'Once the laminated pouch is opened, blister strips should be stored in the outer box below 30°C' should be taken.

Product literature

The SmPCs, PILs and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) forms

The MAA forms are pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossiers.

Quality conclusion

There are no objections to the approval of Perindopril/Indapamide 2mg/0.625 mg and 4mg/1.25 mg Tablets from a quality point of view.

Non clinical aspects**Non clinical overview**

The pharmacodynamic, pharmacokinetic and toxicological properties of perindopril and indapamide are well known and have been adequately reviewed in the non-clinical overview. The absence of new non clinical studies is acceptable for these applications.

Expert report

The non clinical overview has been written by an appropriately qualified person. The report refers to 154 publications up to the year 2008. In view of the fact that the pharmacotoxicological properties of perindopril and indapamide are well known, the overview is acceptable

Environmental risk assessment

A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all perindopril-

and indapamide-containing products, which in turn is unlikely to increase exposure of the environment to these drug substances.

Product literature

The product literature is acceptable from a non clinical point of view.

Non clinical conclusion

There are no objections to the approval of Perindopril/Indapamide 2mg/0.625 mg and 4mg/1.25 mg Tablets from a non clinical point of view.

Clinical aspects

Pharmacokinetic studies

Detailed pharmacology was not investigated as these products are well known in clinical practice. A bioequivalence study has been submitted in support of these applications.

Methods

Study design

This was a single centre, randomised, open-label, 2-way crossover, bioequivalence study of Perindopril/Indapamide 4mg/1.25 mg Tablets and Coversyl Plus (UK reference product) following a 4mg/1.25 mg dose in healthy subjects under fasting conditions. The applicant has given an undertaking that the study was conducted in accordance with GCP and GLP guidelines.

The washout period was 42 days and the sampling period was up to 120 hours post dose. Both parent compound and metabolite were measured for perindopril.

Test and reference products

Test Product: Perindopril/Indapamide 4mg/1.25 mg Tablets
Strength: 4mg/1.25mg

Reference Product: Coversyl Plus tablets
Strength: 4mg/1.25mg

The reference product used in the bioequivalence study is appropriate.

Population studied

A total of 36 subjects (5 females and 31 males) were enrolled and randomised in the study. One subject dropped out and there were no withdrawals. In all, 35 subjects completed the study. The number of subjects that completed the study was reasonable.

Analytical methods

The analytical methods used are acceptable.

Pharmacokinetic variables

The primary criteria for bioequivalence were AUC_{0-t} , AUC_{0-inf} and C_{max} , for perindopril, perindoprilat and indapamide. In addition, residual area, T_{max} , $T_{1/2el}$ and Kel were also evaluated.

The primary variables used to determine bioequivalence were in line with the recommendations in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4 and acceptable.

Statistical methods

The criteria for bioequivalence was 90% geometric confidence intervals of the ratio of least-squares means to be within 80–125%. Data from perindoprilat were used as supportive data.

Parametric ANOVA on AUC_{0-inf} , C_{max} , $T_{1/2el}$ and Kel , geometric confidence intervals for AUC_{0-t} , AUC_{0-inf} and C_{max} and non-parametric test (Wilcoxon) for T_{max} were determined. Covariates in the ANOVA model: sequence, subject within sequence, period and treatment; and Ln-transformed parameters for AUC_{0-t} , AUC_{0-inf} and C_{max} were calculated.

The statistical methods used were appropriate.

Results

The results of the bioequivalence study are shown in the tables below:

(a) Perindopril

Perindopril – Indapamide 4mg/1.25 mg tablets Least Squares Geometric Means, Ratio of Means, and 90% confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t} (pg.h/mL)	36922.08	38157.17	96.76	93.44 – 100.20
AUC_{∞} (pg.h/mL)	37581.55	38824.07	96.80	93.54 – 100.17
C_{max} (pg/mL)	33582.49	37090.24	90.54	85.09 – 96.34

(b) Perindoprilat

Perindopril – Indapamide 4mg/1.25 mg tablets Least Squares Geometric Means, Ratio of Means, and 90% confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.

AUC_{0-120h} (pg.h/mL)	139578.51	140084.88	99.64	96.12 – 103.28
C_{max} (ng/mL)	4498.62	4426.08	101.64	94.39 – 109.45

(c) Indapamide

Perindopril – Indapamide 4mg/1.25 mg tablets Least Squares Geometric Means, Ratio of Means, and 90% confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t} (ng.h/mL)	921.34	874.95	105.30	102.41 – 108.27
AUC_∞ (ng.h/mL)	941.85	896.09	105.11	102.14 – 108.15
C_{max} (ng/mL)	49.37	52.02	94.91	89.66 – 100.46

A total of 51 TEAE (treatment emergent adverse events) were reported in 23 subjects. The most common adverse event was blood pressure decrease. The safety profiles of perindopril and indapamide are well known as they have been in clinical use for many years.

Biowaiver

A biowaver is sought for the lower strength product, Perindopril/Indapamide 2mg/0.625 mg Tablets, as the kinetics of perindopril is linear. Biowaver for the lower strength tablet is acceptable. The results of the bioequivalence study can be extrapolated to the lower strength.

Pharmacokinetic conclusion

Based on the submitted bioequivalence study, Perindopril/Indapamide 4mg/1.25 mg Tablets is considered bioequivalent to Coversyl PLUS.

The results of the study with the 4mg/1.25mg formulation can be extrapolated to the 2mg/0.625 strength product, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacodynamic studies

No new data has been submitted and none is required. This is acceptable for generic applications.

Additional data

The dissolution profiles of the proposed product and the UK reference product used in bioequivalence study have been shown to be comparable.

Clinical efficacy and safety

No new efficacy data are presented and none is required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of perindopril and indapamide.

Pharmacovigilance system

The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk management plan

No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for these applications.

Expert report

A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of the clinical part of the dossier.

Product literature

All product literature (SmPCs, PIL and labelling) is medically satisfactory.

Clinical conclusion

The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval is recommended from the clinical point of view.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Perindopril/Indapamide 2mg/0.625 mg and 4mg/1.25 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

The use of perindopril and indapamide in the treatment of high blood pressure is well established. Bioequivalence has been demonstrated between the applicant's Perindopril/Indapamide 2mg/0.625 mg and 4mg/1.25 mg Tablets and the reference products. New efficacy data is, therefore, not needed.

SAFETY

No new or unexpected safety concerns arise from these applications.

The SmPCs and PILs are satisfactory and consistent with those of the reference products. Satisfactory labelling has also been submitted.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with perindopril and indapamide is considered to have demonstrated the therapeutic value of the compound. The benefit: risk ratio is, therefore, considered to be acceptable. Marketing Authorisations should be granted.