Public Assessment Report
Decentralised Procedure

Pritnox 2mg, 4mg and 8mg Tablets
Peryl 2mg, 4mg and 8mg Tablets
Perilex 4mg and 8mg Tablets

Perindopril tert-butylamine

UK/H/1625/001-3/DC
UK/H/3097/001-3/DC
UK/H/3119/001-2/DC

UK licence no: PL 33815/0001-3, 0006-10

Galex DD
LAY SUMMARY

MHRA granted marketing authorisations for the medicinal products named Pritnox, Peryl and Perilex Tablets on 18th August 2010.

Pritnox, Peryl and Perilex are names for medicines containing the active ingredient, perindopril. The tablets are available in different strengths in order to enable the most appropriate dose to be administered.

The strengths approved contain perindopril 2, 4 and 8mg.

These medicines are available on a prescription from your doctor and are used to treat a number of different conditions:

- to treat high blood pressure (hypertension)
- To reduce the risk of heart problems, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

In addition, the tablets containing perindopril 2 and 4mg are also approved to treat:

- heart failure (A condition where the heart is unable to pump enough to meet the body’s needs)

Perindopril belongs to a class of medicines called ACE inhibitors.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pritnox and Peryl 2, 4 and 8mg Tablets and Perilex 4 and 8mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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| **MA Holder** | Galex DD  
Tisinska Ulica 29G  
Murska Sobota  
SI-9000  
Slovenia |
| **RMS** | UK |
| **CMS** | UK/H/1625/001/DC: DK, FR, LU, NL  
UK/H/1625/002-3/DC: BE, CZ, DK, FI, FR, HU, IT, LU, NL, PL, PT, SK  
UK/H/3097/001-3/DC: BG, CZ, HU, PL, RO, SK  
UK/H/3119/001-2/DC: CZ, EE, EL, HU, LT, LV, PL, SI, SK |
| **Procedure Numbers** | UK/H/1625/001-3/DC  
UK/H/3097/001-3/DC  
UK/H/3119/001-2/DC |
| **Timetable** | Day 210 – 19th July 2010 |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Pritnox 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains, 2 mg perindopril tert-butylamine, equivalent to 1.773 mg perindopril as sodium salt (formed in situ) and equivalent to 1.669 mg of perindopril.
2 mg: Also contains lactose anhydrous 60.953 mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
2 mg: White to creamy white, oblong tablets with a score line on each side. An imprint “2” is located on one side of the score line and on each face of the tablet. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension:
Treatment of hypertension
Heart failure:
Treatment of symptomatic heart failure
Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration
Route of administration: For oral use.
It is recommended that perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.
Hypertension:
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
Symptomatic heart failure:
It is recommended that perindopril, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased after2 weeks to 4 mg once daily, if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see 4.4). Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with perindopril: Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with perindopril (see section 4.4).

**Stable coronary artery disease:**
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated. Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

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

### Table 1: dosage adjustment in renal impairment

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Cl_{\text{Cr}} \geq 60 )</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>( 30 &lt; Cl_{\text{Cr}} &lt; 60 )</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>( 15 &lt; Cl_{\text{Cr}} &lt; 30 )</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients*, ( Cl_{\text{Cr}} &lt; 15 )</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

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

**Children and adolescents** (less than 18 years of age):
Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

### 4.3 Contraindications
Hypersensitivity to Perindopril, to any of the excipients or to any other ACE inhibitor;
History of angioedema associated with previous ACE inhibitor therapy;
Hereditary or idiopathic angioedema;
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

### 4.4 Special warnings and precautions for use

#### Stable coronary artery disease:
If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation. Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

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

Impairment of renal function:

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

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or perindopril may be required.

Haemodialysis patients:

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

Kidney transplantation:

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

Hypersensitivity/Angioedema:

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see 4.8). This may occur at any time during therapy. In such cases, perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.
Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

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

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

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

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

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium containing salt substitutes is generally not recommended (see 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is
diagnosed, treatment with ACE inhibitors should be stopped immediately, and if appropriate, alternative therapy should be started. (see sections 4.3 and 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics:
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

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

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥ 3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:
Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

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

Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human 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 also sections 4.3 and 4.4).

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

4.7 Effects on ability to drive and use machines

Pritnox has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

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

<p>| Very common (≥1/10); common (≥1/100, &lt;1/10); uncommon (≥1/1000, &lt;1/100); rare (≥1/10000, &lt;1/1000); very rare (&lt;1/10000), not known (cannot be estimated from the available data) |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Blood and the lymphatic system disorders         | decreases in haemoglobin and haematocrit,       |                   | hypoglycaemia (see sections 4.4 and 4.5).       |
|                                                 | thrombocytopenia, leucopenia/neutropenia, a,     |                   |                                                 |
|                                                 | agranulocytosis or pancytopenia.                 |                   |                                                 |
|                                                 | In patients with a congenital deficiency of G6PDH, |
|                                                 | haemolytic anaemia has been reported (see section 4.4) |
| Metabolism and nutrition disorders               | mood or sleep disturbances                      |                   |                                                 |
| Psychiatric disorders                            |                                                 |                   |                                                 |</p>
<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>headache, dizziness, vertigo, paresthaesia</th>
<th>confusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td>vision disturbance</td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>tinnitus</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hypotension and effects related to hypotension</td>
<td>stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4). vasculitis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>arrhythmia, angina pectoris and myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4).</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>cough, dyspnoea bronchospasm</td>
<td>eosinophilic pneumonia, rhinitis</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation</td>
<td>dry mouth pancreatitis</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>hepatitis either cytolytic or cholestatic (see section 4.4)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, pruritus angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).</td>
<td>erythema multiforme</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>muscle cramps</td>
<td></td>
</tr>
</tbody>
</table>

Renal and urinary disorders | Renal insufficiency | Acute renal failure
---|---|---
Reproductive system and breast disorders | Impotence
General disorders | Asthenia | Sweating

**Investigations:**
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin has been reported rarely.

**Clinical trials:**
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

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

The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (see 4.4) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

### 5 PHARMACOLOGICAL PROPERTIES
#### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitors, plain; ATC code: C09A A04

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

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

**Hypertension:**
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects.
The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy. In man, Perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries. An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Heart failure:
Perindopril reduces cardiac work by a decrease in pre-load and after-load. Studies in patients with heart failure have demonstrated: decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2 mg of Perindopril tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108). The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers. The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001). In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties
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 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 to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the 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).
5.3 Preclinical safety data
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.
No mutagenicity has been observed in in vitro or in vivo studies.
Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have also been observed.
No carcinogenicity has been observed in long term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose Anhydrous,
Maize Starch,
Microcrystalline Cellulose,
Talc
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25° C. Store in the original container in order to protect from light

6.5 Nature and contents of container
Aluminium/Aluminium blister.
Pack sizes:
10 tablets
30 tablets
60 tablets
90 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER
Galex d.d.
Tišinska ulica 29g
9000 Murzka Sobota
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 33815/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/08/2010

10 DATE OF REVISION OF THE TEXT
18/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Pritnox 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.546 mg perindopril as sodium salt (formed in situ) and equivalent to 3.338 mg of perindopril.
4 mg: Also contains lactose anhydrous 60.559 mg.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
4 mg: White to creamy, oblong tablets with a score line on each side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension:
Treatment of hypertension
Heart failure:
Treatment of symptomatic heart failure
Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration
Route of administration: For oral use.
It is recommended that perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.
Hypertension:
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).

Symptomatic heart failure:
It is recommended that perindopril, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased after 2 weeks to 4 mg once daily, if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see 4.4).
Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with perindopril: Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with perindopril (see section 4.4).

Stable coronary artery disease:
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated. Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

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

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClCR ≥ 60</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>30 &lt; ClCR&lt; 60</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>15 &lt; ClCR&lt; 30</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients*, ClCR&lt; 15</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

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

Children and adolescents (less than 18 years of age):
Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

4.3 Contraindications
Hypersensitivity to Perindopril, to any of the excipients or to any other ACE inhibitor; History of angioedema associated with previous ACE inhibitor therapy; Hereditary or idiopathic angioedema; Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use
Stable coronary artery disease:
If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

**Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:**
As with other ACE inhibitors, perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

**Impairment of renal function:**
In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient’s creatinine clearance (see 4.2) and then as a function of the patient’s response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see 4.8).
In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or perindopril may be required.

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

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

**Hypersensitivity/Angioedema:**
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see 4.8). This may occur at any time during therapy. In such cases, perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.
Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

**Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:**
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.
Anaphylactic reactions during desensitisation:
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (eg. sore throat, fever).

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

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

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

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

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium containing salt substitutes is generally not recommended (see 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).

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

Diuretics:
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

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

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors. Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:
Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

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

4.6 Pregnancy and lactation

Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human 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 also sections 4.3 and 4.4).

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

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

### 4.8 Undesirable effects
The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
<td>decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis or pancytopenia. In patients with a congenital deficiency of G6PDH, haemolytic anaemia has been reported (see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>hypoglycaemia (see sections 4.4 and 4.5).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>mood or sleep disturbances</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>headache, dizziness, vertigo, paresthesia</td>
<td>confusion</td>
<td></td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>vision disturbance</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td>tinnitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>hypotension and effects related to hypotension</td>
<td>stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).</td>
<td>vasculitis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>arrhythmia, angina pectoris and myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>cough, dyspnoea, bronchospasm, eosinophilic pneumonia, rhinitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation, dry mouth, pancreatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>hepatitis either cytolytic or cholestatic (see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, pruritus, angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4), erythema multiforme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>muscle cramps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>renal insufficiency, acute renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>impotence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>asthenia, sweating</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigations:
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin has been reported rarely.

Clinical trials:
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough,
hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose
Limited data are available for overdose in humans. Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (see 4.4) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitors, plain; ATC code: C09A A04

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

Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy. In man, Perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries. An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Heart failure:
Perindopril reduces cardiac work by a decrease in pre-load and after-load. Studies in patients with heart failure have demonstrated: decreased left and right ventricular filling pressures, reduced total peripheral vascular resistance, increased cardiac output and improved cardiac index. In comparative studies, the first administration of 2 mg of Perindopril tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

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

The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties

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 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 to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the 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).

5.3 Preclinical safety data

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

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

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

No carcinogenicity has been observed in long term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Anhydrous,
Maize Starch,
Microcrystalline Cellulose,
Talc
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
6.4 **Special precautions for storage**
Do not store above 25° C. Store in the original container in order to protect from light.

6.5 **Nature and contents of container**
Aluminium/Aluminium blister.
Pack sizes:
- 10 tablets
- 30 tablets
- 60 tablets
- 90 tablets
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 33815/0002

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
18/08/2010

10 **DATE OF REVISION OF THE TEXT**
18/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Pritnox 8 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains, 8 mg perindopril tert-butylamine, equivalent to 7.092mg perindopril as sodium salt (formed in situ) and equivalent to 6.676 mg of perindopril.
Also contains lactose anhydrous 121.118 mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
White to creamy, round, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
8mg:
Hypertension:
Treatment of hypertension
Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration
Route of administration: For oral use.
It is recommended that perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.
Not all mentioned posologies are possible with the product in this SmPC.
Hypertension:
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
Stable coronary artery disease:
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.
Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.
Dosage adjustment in renal impairment:
Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:
Table 1: dosage adjustment in renal impairment

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClCR ≥ 60</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>30 &lt; ClCR &lt; 60</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>15 &lt; ClCR &lt; 30</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients*, ClCR &lt; 15</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

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

Children and adolescents (less than 18 years of age):
Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

4.3 Contraindications
Hypersensitivity to Perindopril, to any of the excipients or to any other ACE inhibitor;
History of angioedema associated with previous ACE inhibitor therapy;
Hereditary or idiopathic angioedema;
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use
Stable coronary artery disease:
If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:
As with other ACE inhibitors, perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

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

In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or perindopril may be required.

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

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

Hypersensitivity/Angioedema:
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see 4.8). This may occur at any time during therapy. In such cases, perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3). Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procarbazine, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic
therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g., sore throat, fever).

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

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

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

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

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium containing salt substitutes is generally not recommended (see 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).

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

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics:
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore the combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.
Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.
Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:
Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

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

4.6 Pregnancy and lactation

Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human 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 also sections 4.3 and 4.4).

Lactation:
Because no information is available regarding the use of Pritnox during breastfeeding, Pritnox is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
4.7 Effects on ability to drive and use machines
Pritnox has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication. As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects
The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency

| Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data) |
| --- | --- | --- | --- |
| Blood and the lymphatic system disorders | common | uncommon | very rare |
| decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis or pancytopenia. In patients with a congenital deficiency of G6PDH, haemolytic anaemia has been reported (see section 4.4) |  |
| Metabolism and nutrition disorders |  |  | hypoglycaemia (see sections 4.4 and 4.5). |
| Psychiatric disorders | mood or sleep disturbances |  |  |
| Nervous system disorders | headache, dizziness, vertigo, paresthaesia | confusion |  |
| Eye disorders | vision disturbance |  |  |
| Ear and labyrinth disorders | tinnitus |  |  |
| Vascular disorders | hypotension and effects related to hypotension | stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4). | vasculitis |
| Cardiac disorders | arrhythmia, angina pectoris and myocardial infarction |  |  |
| Respiratory, thoracic and mediastinal disorders | cough, dyspnoea | bronchospasm | eosinophilic pneumonia, rhinitis |
| Gastrointestinal disorders | nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation | dry mouth | pancreatitis |
| Hepato-biliary disorders | | | hepatitis either cytolytic or cholestatic (see section 4.4) |
| Skin and subcutaneous tissue disorders | rash, pruritus | angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4). | erythema multiforme |
| Musculoskeletal, connective tissue and bone disorders | muscle cramps | | |
| Renal and urinary disorders | | renal insufficiency | acute renal failure |
| Reproductive system and breast disorders | | impotence | |
| General disorders | asthenia | sweating | |

Investigations:
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin has been reported rarely.

Clinical trials:
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients,
angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose
Limited data are available for overdose in humans.
Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.
The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (see 4.4) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitors, plain; ATC code: C09A A04

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

Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy.
In man, Perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries. An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108). The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers. The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butyramine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute
reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).
In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties
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 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 to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the 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).

5.3 Preclinical safety data
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.
No mutagenicity has been observed in in vitro or in vivo studies.
Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have also been observed.
No carcinogenicity has been observed in long term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose Anhydrous,
Maize Starch,
Microcrystalline Cellulose,
Talc
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25° C. Store in the original container in order to protect from light

6.5 Nature and contents of container
Aluminium/Aluminium blister.
Pack sizes:
10 tablets
30 tablets
60 tablets
6.6 Special precautions for disposal
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 33815/0003

9 DATE OF FIRST AUTHOURISATION/RENEWAL OF THE AUTHORISATION
18/08/2010

10 DATE OF REVISION OF THE TEXT
18/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Peryl 2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains, 2 mg perindopril tert-butylamine, equivalent to 1.773 mg perindopril as sodium salt (formed in situ) and equivalent to 1.669 mg of perindopril.
2 mg: Also contains lactose anhydrous 60.953 mg.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
2 mg: White to creamy white, oblong tablets with a score line on each side. An imprint “2” is located on one side of the score line and on each face of the tablet. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension:
Treatment of hypertension
Heart failure:
Treatment of symptomatic heart failure
Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration
Route of administration: For oral use.
It is recommended that perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.
Hypertension:
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
Symptomatic heart failure:
It is recommended that perindopril, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased after 2 weeks to 4 mg once daily, if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see 4.4).
Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with perindopril: Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with perindopril (see section 4.4).

Stable coronary artery disease:
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated. Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

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

Table 1: dosage adjustment in renal impairment

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl(\text{CR}) ≥ 60</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>30 &lt; Cl(\text{CR}) &lt; 60</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>15 &lt; Cl(\text{CR}) &lt; 30</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients*, Cl(\text{CR}) &lt; 15</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

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

Children and adolescents (less than 18 years of age):
Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

4.3 Contraindications
Hypersensitivity to Perindopril, to any of the excipients or to any other ACE inhibitor;
History of angioedema associated with previous ACE inhibitor therapy;
Hereditary or idiopathic angioedema;
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use
Stable coronary artery disease:
If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

**Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:**
As with other ACE inhibitors, perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

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

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or perindopril may be required.

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

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

**Hypersensitivity/Angioedema:**
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see 4.8). This may occur at any time during therapy. In such cases, perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

**Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:**
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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

**Hepatic failure:**
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

**Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:**
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (eg. sore throat, fever).

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

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

**Surgery/Anaesthesia:**
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

**Hyperkalaemia:**
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

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

**Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:**
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium containing salt substitutes is generally not recommended (see 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).

**Excipients:**
Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency should not take this medicinal product.
4.5 Interaction with other medicinal products and other forms of interaction

Diuretics:
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

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

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors. Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:
Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.
Gold:
Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

4.6 Pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to ACE inhibitor/therapy during the second and third trimesters is known to induce human 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 also sections 4.3 and 4.4).

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

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

**4.8 Undesirable effects**
The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency:

| Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data) |
|---|---|---|---|
| Blood and the lymphatic system disorders | common | uncommon | very rare |
| decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis or pancytopenia. In patients with a congenital deficiency of G6PDH, haemolytic anaemia has been reported (see section 4.4) |
| Metabolism and nutrition disorders | | | hypoglycaemia (see sections 4.4 and 4.5). |
| Psychiatric disorders | mood or sleep disturbances |
| Nervous system disorders | headache, dizziness, vertigo, paresthesia | confusion |
| Eye disorders | vision disturbance |
| Ear and labyrinth disorders | tinnitus |  |  |
|-----------------------------|----------|-----------------------------|
| Vascular disorders          | hypotension and effects related to hypotension | stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4). | vasculitis |
| Cardiac disorders           | arrhythmia, angina pectoris and myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4). |  |  |
| Respiratory, thoracic and mediastinal disorders | cough, dyspnoea bronchospasm | eosinophilic pneumonia, rhinitis |  |
| Gastro-intestinal disorders | nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation | dry mouth | pancreatitis |
| Hepato-biliary disorders    |  | hepatitis either cytolytic or cholestatic (see section 4.4) |  |
| Skin and subcutaneous tissue disorders | rash, pruritus angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4). | erythema multiforme |  |
| Musculoskeletal, connective tissue and bone disorders | muscle cramps |  |  |
| Renal and urinary disorders | renal insufficiency | acute renal failure |  |
Reproductive system and breast disorders | impotence
---|---
General disorders | asthenia | sweating

Investigations:
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin has been reported rarely.

Clinical trials:
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose
Limited data are available for overdose in humans.
Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.
The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (see 4.4) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitors, plain; ATC code: C09A A04

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

Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed.
Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate.
Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects.
The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis.
Discontinuation of treatment does not lead to a rebound effect.
Perindopril reduces left ventricular hypertrophy.
In man, Perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries. An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

**Heart failure:**
Perindopril reduces cardiac work by a decrease in pre-load and after-load. Studies in patients with heart failure have demonstrated:
- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.
In comparative studies, the first administration of 2 mg of Perindopril tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

**Patients with stable coronary artery disease:**
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108). The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers.

The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties
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 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 to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the 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).

5.3 Preclinical safety data
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.
No mutagenicity has been observed in **in vitro** or **in vivo** studies.
Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in
rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have also been observed.
No carcinogenicity has been observed in long term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose Anhydrous,
Maize Starch,
Microcrystalline Cellulose,
Talc
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container in order to protect from light.

6.5 Nature and contents of container
Aluminium/Aluminium blister.
Pack sizes:
30 tablets
60 tablets
90 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORITY
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

8 MARKETING AUTHORITY NUMBER(S)
PL 33815/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
18/08/2010

10 DATE OF REVISION OF THE TEXT
18/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Peryl 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.546 mg perindopril as sodium salt (formed in situ) and equivalent to 3.338 mg of perindopril.
4 mg: Also contains lactose anhydrous 60.559 mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
4 mg: White to creamy, oblong tablets with a score line on each side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension:
Treatment of hypertension
Heart failure:
Treatment of symptomatic heart failure
Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration
Route of administration: For oral use.
It is recommended that perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.
Hypertension:
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
Symptomatic heart failure:
It is recommended that perindopril, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased after 2 weeks to 4 mg once daily, if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see 4.4).
Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with perindopril. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with perindopril (see section 4.4).

**Stable coronary artery disease:**
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated. Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

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

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClCr ≥ 60</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>30 &lt; ClCr &lt; 60</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>15 &lt; ClCr &lt; 30</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients*, ClCr &lt; 15</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

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

**Children and adolescents** (less than 18 years of age); Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

**4.3 Contraindications**
Hypersensitivity to Perindopril, to any of the excipients or to any other ACE inhibitor; History of angioedema associated with previous ACE inhibitor therapy; Hereditary or idiopathic angioedema; Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

**4.4 Special warnings and precautions for use**
**Stable coronary artery disease:**
If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation. Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:
As with other ACE inhibitors, perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Impairment of renal function:
In cases of renal impairment (creatinine clearance < 60 ml/min) the initial perindopril dosage should be adjusted according to the patient’s creatinine clearance (see 4.2) and then as a function of the patient’s response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see 4.8).
In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.
Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or perindopril may be required.

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

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

Hypersensitivity/Angioedema:
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see 4.8). This may occur at any time during therapy. In such cases, perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.
Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3).
Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.
Anaphylactic reactions during desensitisation:
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (eg. sore throat, fever).

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

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

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

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

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium containing salt substitutes is generally not recommended (see 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).

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

Diuretics:
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

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

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:
Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

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

4.6 Pregnancy and lactation

Pregnancy:

The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to ACE inhibitor/therapy during the second and third trimesters is known to induce human 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 also sections 4.3 and 4.4).

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

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

### 4.8 Undesirable effects
The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency

<table>
<thead>
<tr>
<th>Very common (≥1/10); common (≥1/100, &lt;1/10); uncommon (≥1/1000, &lt;1/100); rare (≥1/10000, &lt;1/1000); very rare (&lt;1/10000), not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Vascular disorders</td>
</tr>
<tr>
<td>Cardiac disorders</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
</tr>
</tbody>
</table>
Reproductive system and breast disorders

<table>
<thead>
<tr>
<th>Impotence</th>
</tr>
</thead>
</table>

General disorders

<table>
<thead>
<tr>
<th>Asthenia</th>
<th>Sweating</th>
</tr>
</thead>
</table>

Investigations:
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin has been reported rarely.

Clinical trials:
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose
Limited data are available for overdose in humans. Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (see 4.4) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitors, plain; ATC code: C09A A04
Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikreinkinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).
Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro.

Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100% of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy.
In man, Perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery
elasticity and decreases the media: lumen ratio of small arteries.
An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination
of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic
treatment.
Heart failure:
Perindopril reduces cardiac work by a decrease in pre-load and after-load.
Studies in patients with heart failure have demonstrated:
decreased left and right ventricular filling pressures,
reduced total peripheral vascular resistance,
increased cardiac output and improved cardiac index.
In comparative studies, the first administration of 2 mg of Perindopril tert-butylamine to patients with
mild to moderate heart failure was not associated with any significant reduction of blood pressure as
compared to placebo.
Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled
clinical trial lasting 4 years.
Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to
perindopril 8 mg (n=6110) or placebo (n=6108).
The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart
failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary
revascularisation. Most of the patients received the study medication on top of conventional therapy
including platelet inhibitors, lipid lowering agents and beta-blockers.
The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial
infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-
butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute
reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] –
p<0.001).
In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of
2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was
observed by comparison to placebo.

5.2 Pharmacokinetic properties
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 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 to
plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.
Perindoprilat is eliminated in the urine and the 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).

5.3 Preclinical safety data
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible
damage.
No mutagenicity has been observed in in vitro or in vivo studies.
Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity
or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to
induce adverse effects on late fetal development, resulting in fetal death and congenital effects in
rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have also been observed. No carcinogenicity has been observed in long term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose Anhydrous,
Maize Starch,
Microcrystalline Cellulose,
Talc
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container in order to protect from light

6.5 Nature and contents of container
Aluminium/Aluminium blister.
Pack sizes:
30 tablets
60 tablets
90 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 33815/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/08/2010

10 DATE OF REVISION OF THE TEXT
18/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Peryl 8 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains, 8 mg perindopril tert-butylamine, equivalent to 7.092mg perindopril as sodium salt (formed in situ) and equivalent to 6.676 mg of perindopril.
Also contains lactose anhydrous 121.118 mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
White to creamy, round, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
8mg:
Hypertension:
Treatment of hypertension
Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration
Route of administration: For oral use.
It is recommended that perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.
Not all mentioned posologies are possible with the product in this SmPC.
Hypertension:
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
Stable coronary artery disease:
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.
Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.
Dosage adjustment in renal impairment:
Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:

55
Table 1: dosage adjustment in renal impairment

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Cl}_{\text{Cr}} \geq 60$</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>$30 &lt; \text{Cl}_{\text{Cr}} &lt; 60$</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>$15 &lt; \text{Cl}_{\text{Cr}} &lt; 30$</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>$\text{Haemodialysed patients*, } \text{Cl}_{\text{Cr}} &lt; 15$</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

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

Children and adolescents (less than 18 years of age):
Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

4.3 Contraindications
Hypersensitivity to Perindopril, to any of the excipients or to any other ACE inhibitor;
History of angioedema associated with previous ACE inhibitor therapy;
Hereditary or idiopathic angioedema;
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use
Stable coronary artery disease:
If an episode of unstable angina pectoris (major or not) occurs during the first month of perindopril treatment, a careful appraisal of the benefit/risk should be performed before treatment continuation.

Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:
As with other ACE inhibitors, perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

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

In patients with symptomatic heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or perindopril may be required.

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

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

Hypersensitivity/Angioedema:
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see 4.8). This may occur at any time during therapy. In such cases, perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic
therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (eg. sore throat, fever).

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

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

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydation, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

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

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium containing salt substitutes is generally not recommended (see 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).

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

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics:
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. Potassium sparing diuretics (e.g. spironolacltone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore the combination of perindopril with the above-mentioned drugs is not recommended (see section 4.4). If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.
Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:
Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

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

4.6 Pregnancy and lactation

Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor/therapy during the second and third trimesters is known to induce human 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 also sections 4.3 and 4.4).

Lactation:
Because no information is available regarding the use of Peryl during breastfeeding, Peryl is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.
4.7 Effects on ability to drive and use machines
Peryl has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.
As a result the ability to drive or operate machinery may be impaired.

4.8 Undesirable effects
The following undesirable effects have been observed during treatment with perindopril and ranked under the following frequency

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Common</th>
<th>Uncommon</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td></td>
<td>decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis or pancytopenia. In patients with a congenital deficiency of G6PDH, haemolytic anaemia has been reported (see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>hypoglycaemia (see sections 4.4 and 4.5).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>mood or sleep disturbances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, dizziness, vertigo, paresthesia</td>
<td></td>
<td>confusion</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>vision disturbance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>tinnitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hypotension and effects related to hypotension</td>
<td></td>
<td>stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).</td>
<td>vasculitis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>arrhythmia, angina pectoris and myocardial infarction possibly secondary to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>System</td>
<td>Symptoms</td>
<td>Excessive Hypotension in High-Risk Patients (see Section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>cough, dyspnoea, bronchospasm, eosinophilic pneumonia, rhinitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>hepatitis either cytolytic or cholestatic (see Section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, pruritus, angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see Section 4.4)</td>
<td>erythema multiforme</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>muscle cramps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>renal insufficiency, acute renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>impotence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>asthenia, sweating</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Investigations:**
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin has been reported rarely.

**Clinical trials:**
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.
4.9 Overdose
Limited data are available for overdose in humans. Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (see 4.4) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitors, plain; ATC code: C09A A04

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

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

Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy. In man, Perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries. An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108). The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers. The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butyramidine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).
In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties
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 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 to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent.

Perindoprilat is eliminated in the urine and the 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).

5.3 Preclinical safety data
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

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

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

No carcinogenicity has been observed in long term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose Anhydrous,
Maize Starch,
Microcrystalline Cellulose,
Talc
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container in order to protect from light

6.5 Nature and contents of container
Aluminium/Aluminium blister.

Pack sizes:
30 tablets
60 tablets
90 tablets
Not all pack sizes may be marketed.
6.6 Special precautions for disposal
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 33815/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/08/2010

10 DATE OF REVISION OF THE TEXT
18/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Perilex 4 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.546 mg perindopril as sodium salt (formed in situ) and equivalent to 3.338 mg of perindopril.
4 mg: Also contains lactose anhydrous 60.559 mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
4 mg: White to creamy, oblong tablets with a score line on each side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypertension:
Treatment of hypertension
Heart failure:
Treatment of symptomatic heart failure
Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration
Route of administration: For oral use.
It is recommended that perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.
Hypertension:
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.

Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with perindopril (see section 4.4). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).

Symptomatic heart failure:
It is recommended that perindopril, generally associated with a non-potassium-sparing diuretic and/or digoxin and/or a beta blocker, be introduced under close medical supervision with a recommended starting dose of 2 mg taken in the morning. This dose may be increased after 2 weeks to 4 mg once daily, if tolerated. The dose adjustment should be based on the clinical response of the individual patient.
In severe heart failure and in other patients considered to be at high risk (patients with impaired renal function and a tendency to have electrolyte disturbances, patients receiving simultaneous treatment with diuretics and/or treatment with vasodilating agents), treatment should be initiated under careful supervision (see 4.4).
Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy should have these conditions corrected, if possible, prior to therapy with perindopril. Blood pressure, renal function and serum potassium should be monitored closely, both before and during treatment with perindopril (see section 4.4).

**Stable coronary artery disease:**
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated. Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.

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

### Table 1: dosage adjustment in renal impairment

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl&lt;sub&gt;Cr&lt;/sub&gt; ≥ 60</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>30 &lt; Cl&lt;sub&gt;Cr&lt;/sub&gt; &lt; 60</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>15 &lt; Cl&lt;sub&gt;Cr&lt;/sub&gt; &lt; 30</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients*, Cl&lt;sub&gt;Cr&lt;/sub&gt; &lt; 15</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

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

**Children and adolescents** (less than 18 years of age):
Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

### 4.3 Contraindications

Hypersensitivity to Perindopril, to any of the excipients or to any other ACE inhibitor;
History of angioedema associated with previous ACE inhibitor therapy;
Hereditary or idiopathic angioedema;
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

### 4.4 Special warnings and precautions for use

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

**Hypotension:**
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.
In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

**Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:**

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

**Impairment of renal function:**

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

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or perindopril may be required.

**Haemodialysis patients:**

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

**Kidney transplantation:**

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

**Hypersensitivity/Angioedema:**

Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see 4.8). This may occur at any time during therapy. In such cases, perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3).

Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

**Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:**

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Achromia:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (eg. sore throat, fever).

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

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

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

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

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium containing salt substitutes is generally not recommended (see 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).

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

Diuretics:
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

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

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥ 3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors. Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:
Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.
Gold:
Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

4.6 Pregnancy and lactation

Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to ACE inhibitor/therapy during the second and third trimesters is known to induce human 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 also sections 4.3 and 4.4).

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

### 4.7 Effects on ability to drive and use machines

Perilex has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

As a result the ability to drive or operate machinery may be impaired.

### 4.8 Undesirable effects

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

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Very common (≥1/10); common (≥1/100, &lt;1/10); uncommon (≥1/1000, &lt;1/100); rare (≥1/10000, &lt;1/1000); very rare (&lt;1/10000); not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the lymphatic system disorders</strong></td>
<td>decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis or pancytopenia. In patients with a congenital deficiency of G6PDH, haemolytic anaemia has been reported (see section 4.4)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>hypoglycaemia (see sections 4.4 and 4.5).</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>mood or sleep disturbances</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>headache, dizziness, vertigo, paresthesia</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>vision disturbance</td>
</tr>
</tbody>
</table>

<p>| <strong>Eye disorders</strong> | vision disturbance |</p>
<table>
<thead>
<tr>
<th>Medical Disorders</th>
<th>Symptoms/Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear and labyrinth disorders</td>
<td>tinnitus</td>
<td>stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4).</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hypotension and effects related to hypotension</td>
<td>vasculitis</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>arrhythmia, angina pectoris and myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4).</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>cough, dyspnoea bronchospasm</td>
<td>eosinophilic pneumonia, rhinitis</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation</td>
<td>dry mouth pancreatitis</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td>hepatitis either cytolytic or cholestatic (see section 4.4)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, pruritus angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).</td>
<td>erythema multiforme</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>muscle cramps</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>renal insufficiency</td>
<td>acute renal failure</td>
</tr>
</tbody>
</table>
Reproductive system and breast disorders | impotence
---|---
General disorders | asthenia | sweating

Investigations:
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin has been reported rarely.

Clinical trials:
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.

4.9 Overdose
Limited data are available for overdose in humans. Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (see 4.4) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitors, plain; ATC code: C09A A04

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

Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy.
In man, Perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries. An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

**Heart failure:**
Perindopril reduces cardiac work by a decrease in pre-load and after-load. Studies in patients with heart failure have demonstrated:
- decreased left and right ventricular filling pressures,
- reduced total peripheral vascular resistance,
- increased cardiac output and improved cardiac index.

In comparative studies, the first administration of 2 mg of Perindopril tert-butylamine to patients with mild to moderate heart failure was not associated with any significant reduction of blood pressure as compared to placebo.

**Patients with stable coronary artery disease:**
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108). The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers. The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).

In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

**5.2 Pharmacokinetic properties**
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 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 to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the 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).

**5.3 Preclinical safety data**
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose Anhydrous,
Maize Starch,
Microcrystalline Cellulose,
Talc
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container in order to protect from light

6.5 Nature and contents of container
Aluminium/Aluminium blister.
Pack sizes:
30 tablets
60 tablets
90 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 33815/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/08/2010

10 DATE OF REVISION OF THE TEXT
18/08/2010
1 NAME OF THE MEDICINAL PRODUCT
Perilex 8 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains, 8 mg perindopril tert-butylamine, equivalent to 7.092mg perindopril as sodium salt (formed in situ) and equivalent to 6.676 mg of perindopril.
Also contains lactose anhydrous 121.118 mg
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet
White to creamy, round, biconvex tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
8mg:
Hypertension:
Treatment of hypertension
Stable coronary artery disease:
Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation

4.2 Posology and method of administration
Route of administration: For oral use.
It is recommended that perindopril is taken once daily in the morning before a meal.
The dose should be individualised according to the patient profile (see 4.4) and blood pressure response.
Not all mentioned posologies are possible with the product in this SmPC.
Hypertension:
Perindopril may be used in monotherapy or in combination with other classes of antihypertensive therapy.
The recommended starting dose is 4 mg given once daily in the morning.
Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and/or volume depletion, cardiac decompensation or severe hypertension) may experience an excessive drop in blood pressure following the initial dose. A starting dose of 2 mg is recommended in such patients and the initiation of treatment should take place under medical supervision.
The dose may be increased to 8 mg once daily after one month of treatment.
Symptomatic hypotension may occur following initiation of therapy with perindopril; this is more likely in patients who are being treated concurrently with diuretics. Caution is therefore recommended since these patients may be volume and/or salt depleted.
If possible, the diuretic should be discontinued 2 to 3 days before beginning therapy with perindopril (see section 4.4).
In hypertensive patients in whom the diuretic cannot be discontinued, therapy with perindopril should be initiated with a 2 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of perindopril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.
In elderly patients treatment should be initiated at a dose of 2 mg which may be progressively increased to 4 mg after one month then to 8 mg if necessary depending on renal function (see table below).
Stable coronary artery disease:
Perindopril should be introduced at a dose of 4 mg once daily for two weeks, then increased to 8 mg once daily, depending on renal function and provided that the 4 mg dose is well tolerated.
Elderly patients should receive 2 mg once daily for one week, then 4 mg once daily the next week, before increasing the dose up to 8 mg once daily depending on renal function (see Table 1 “Dosage adjustment in renal impairment”). The dose should be increased only if the previous lower dose is well tolerated.
Dosage adjustment in renal impairment:
Dosage in patients with renal impairment should be based on creatinine clearance as outlined in table 1 below:
Table 1: dosage adjustment in renal impairment

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl(_{CR}) ≥ 60</td>
<td>4 mg per day</td>
</tr>
<tr>
<td>30 &lt; Cl(_{CR}&lt; 60</td>
<td>2 mg per day</td>
</tr>
<tr>
<td>15 &lt; Cl(_{CR}&lt; 30</td>
<td>2 mg every other day</td>
</tr>
<tr>
<td>Haemodialysed patients*, Cl(_{CR}&lt; 15</td>
<td>2 mg on the day of dialysis</td>
</tr>
</tbody>
</table>

* Dialysis clearance of perindoprilat is 70 ml/min. For patients on haemodialysis, the dose should be taken after dialysis.

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

Children and adolescents (less than 18 years of age):
Efficacy and safety of use in children and adolescents have not been established. Therefore, use in children and adolescents is not recommended.

4.3 Contraindications
Hypersensitivity to Perindopril, to any of the excipients or to any other ACE inhibitor;
History of angioedema associated with previous ACE inhibitor therapy;
Hereditary or idiopathic angioedema;
Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

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

Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension (see sections 4.5 and 4.8). In patients with symptomatic heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see 4.2 and 4.8). Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

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

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with perindopril. This effect is anticipated and is usually not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose or discontinuation of perindopril may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:
As with other ACE inhibitors, perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

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

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

In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible...
upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or perindopril may be required.

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

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

Hypersensitivity/Angioedema:
Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril (see 4.8). This may occur at any time during therapy. In such cases, perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3). Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:
Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

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

Hepatic failure:
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see 4.8).

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).
Race:
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

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

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, perindopril may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkalaemia can cause serious, sometimes fatal arrhythmias. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

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

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

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes:
The combination of perindopril and potassium sparing diuretics, potassium supplements or potassium containing salt substitutes is generally not recommended (see 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).

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

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics:
Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

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

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

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

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

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

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

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors. Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates:
Perindopril may be used concomitantly with acetylsalicylic acid (when used as a thrombolytic), thrombolytics, beta-blockers and/or nitrates.

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

4.6 Pregnancy and lactation
Pregnancy:
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Exposure to ACE inhibitor/therapy during the second and third trimesters is known to induce human 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 also sections 4.3 and 4.4).

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

4.7 Effects on ability to drive and use machines
Perilex has no direct influence on the ability to drive and use machines but individual reactions related to low blood pressure may occur in some patients, particularly at the start of treatment or in combination with another antihypertensive medication.

As a result the ability to drive or operate machinery may be impaired.
4.8 Undesirable effects

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

<p>| Very common (≥1/10); common (≥1/100, &lt;1/10); uncommon (≥1/1000, &lt;1/100); rare (≥1/10000, &lt;1/1000); very rare (&lt;1/10000), not known (cannot be estimated from the available data) |
|---|---|---|---|
| Blood and the lymphatic system disorders | decreases in haemoglobin and haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis or pancytopenia. In patients with a congenital deficiency of G6PDH, haemolytic anaemia has been reported (see section 4.4) |  |
| Metabolism and nutrition disorders | hypoglycaemia (see sections 4.4 and 4.5). |  |
| Psychiatric disorders | mood or sleep disturbances |  |
| Nervous system disorders | headache, dizziness, vertigo, paresthesia | confusion |
| Eye disorders | vision disturbance |  |
| Ear and labyrinth disorders | tinnitus |  |
| Vascular disorders | hypotension and effects related to hypotension | stroke, possibly secondary to excessive hypotension in high-risk patients (see section 4.4). vasculitis |
| Cardiac disorders | arrhythmia, angina pectoris and myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4). |  |</p>
<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th>cough, dyspnoea</th>
<th>bronchospasm</th>
<th>eosinophilic pneumonia, rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro- intestinal disorders</td>
<td>nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation</td>
<td>dry mouth</td>
<td>pancreatitis</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
<td>hepatitis either cytolytic or cholestatic (see section 4.4)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash, pruritus</td>
<td>angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx, urticaria (see section 4.4).</td>
<td>erythema multiforme</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>muscle cramps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>renal insufficiency</td>
<td>acute renal failure</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>impotence</td>
<td></td>
</tr>
<tr>
<td>General disorders</td>
<td>asthenia</td>
<td>sweating</td>
<td></td>
</tr>
</tbody>
</table>

Investigations:
Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. Elevation of liver enzymes and serum bilirubin has been reported rarely.

Clinical trials:
During the randomised period of the EUROPA study, only serious adverse events were collected. Few patients experienced serious adverse events: 16 (0.3%) of the 6122 perindopril patients and 12 (0.2%) of the 6107 placebo patients. In perindopril-treated patients, hypotension was observed in 6 patients, angioedema in 3 patients and sudden cardiac arrest in 1 patient. More patients withdrew for cough, hypotension or other intolerance on perindopril than on placebo, 6.0% (n=366) versus 2.1% (n=129) respectively.
4.9 Overdose
Limited data are available for overdose in humans. Symptoms associated with overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdose is intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis. (see 4.4) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ACE inhibitors, plain; ATC code: C09A A04

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

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

Hypertension:
Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100 % of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy.
In man, Perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries. An adjunctive therapy with a thiazide diuretic produces an additive-type of synergy. The combination of an ACE inhibitor and a thiazide also decreases the risk of hypokalaemia induced by the diuretic treatment.

Patients with stable coronary artery disease:
The EUROPA study was a multicentre, international, randomised, double-blind, placebo-controlled clinical trial lasting 4 years. Twelve thousand two hundred and eighteen (12218) patients aged over 18 were randomised to perindopril 8 mg (n=6110) or placebo (n=6108). The trial population had evidence of coronary artery disease with no evidence of clinical signs of heart failure. Overall, 90% of the patients had a previous myocardial infarction and/or a previous coronary revascularisation. Most of the patients received the study medication on top of conventional therapy including platelet inhibitors, lipid lowering agents and beta-blockers. The main efficacy criterion was the composite of cardiovascular mortality, non fatal myocardial infarction and/or cardiac arrest with successful resuscitation. The treatment with 8 mg perindopril tert-butylamine (equivalent to 10 mg perindopril arginine) once daily resulted in a significant absolute reduction in the primary endpoint of 1.9% (relative risk reduction of 20%, 95%CI [9.4; 28.6] – p<0.001).
In patients with a history of myocardial infarction and/or revascularisation, an absolute reduction of 2.2% corresponding to a RRR of 22.4% (95%CI [12.0; 31.6] – p<0.001) in the primary endpoint was observed by comparison to placebo.

5.2 Pharmacokinetic properties
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 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 to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration-dependent. Perindoprilat is eliminated in the urine and the 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).

5.3 Preclinical safety data
In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage.

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

No carcinogenicity has been observed in long term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose Anhydrous,
Maize Starch,
Microcrystalline Cellulose,
Talc
Magnesium Stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25° C. Store in the original container in order to protect from light

6.5 Nature and contents of container
Aluminium/Aluminium blister.
Pack sizes:
30 tablets
60 tablets
90 tablets
Not all pack sizes may be marketed.
6.6 Special precautions for disposal
No special requirements.
Any unused product or waste should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

8 MARKETING AUTHORISATION NUMBER(S)
PL 33815/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
18/08/2010

10 DATE OF REVISION OF THE TEXT
18/08/2010
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pritnox 2&4 mg, tablets
Perindopril tert-butylamine

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 Pritnox 2&4 mg is and what it is used for
2. Before you take Pritnox 2&4 mg
3. How to take Pritnox 2&4 mg
4. Possible side effects
5. How to store Pritnox 2&4 mg
6. Further information

1. WHAT PRITNOX 2&4 mg IS AND WHAT IT IS USED FOR

Pritnox 2&4 mg belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Pritnox 2&4 mg tablets are used:
- to treat high blood pressure (hypertension)
- to treat heart failure (a condition where the heart is unable to pump enough to meet the body's needs).
- To reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

2. BEFORE YOU TAKE PRITNOX 2&4 mg

Do not take Pritnox 2&4 mg
- if you are allergic (hypersensitive) to Perindopril or any of the other ingredients in the tablet or any other ACE inhibitor (see section 6).
- if you have had symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, fainting or dizziness with previous ACE inhibitor treatment or have had these symptoms in any other circumstances (this is a condition called angioedema).
- if you have hereditary tendency to tissue swelling or tissue swelling of unknown origin (hereditary or idiopathic angioedema).
- if you are more than 3 months pregnant. (It is also better to avoid Pritnox 2&4 mg in early pregnancy – see pregnancy section.)

If you think any of the above situations applies to you do not take the tablets. Consult your doctor and take his/her advice.
Take special care with Pritnox 2&4 mg
You should check with your doctor BEFORE taking Pritnox 2&4 mg if you:

- are in risk of an excessive fall in the blood pressure. This may be the case, among others, if you suffer from heart failure, impaired renal function of disorders in the salt and fluid balance, e.g. because you take diuretics (medicines that increase urine production) or keep low-salt diet or as a consequence of vomiting or diarrhoea.
- have aortic stenosis (narrowing of the main blood vessel leading from the heart), mitral valv stenosis (narrowing of heart’s mitral valve), hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood).
- have hypersensitivity reactions or tissue swelling (angioedema) during treatment with Pritnox 2&4 mg or other ACE inhibitors.
- Angioneurotic oedema more frequently occur in patients with black skin colour than in patients with non-black skin colour.
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
- are undergoing LDL-apheresis (which is removal of cholesterol from your blood by a machine)
- have a heart problem.
- have a liver problem.
- have a kidney problem, or have recently had a kidney transplantation
- are receiving dialysis.
- suffer from a collagen disease such as systemic lupus erythematosus or sclerodema.
- are on a salt restricted diet or use salt substitutes which contain potassium.
- suffer from a diabetes which is not well controlled
- you must tell your doctor if you think you are (or might become) pregnant. Pritnox 2&4 mg is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).
- are breast-feeding.

Pritnox 2&4 mg tablets are not recommended for children.

You should also inform your doctor or medical staff that you are taking Pritnox 2&4 mg
- if you had an episode of chest pains (angina pectoris).
- if you are to undergo anaesthesia and/or surgery.
- if you have suffered from recent diarrhoea or vomiting.
- If your blood pressure is not sufficiently lowered due to your ethnic affiliation (particularly in patients with black skin colour).
- If you have a persistent dry cough.
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, herbal or natural products. In particular, you should check with your doctor if you are taking any of the following to be sure that it is safe to take Pritnox 2&4 mg:

- Other medicines for treating high blood pressure including diuretics (water tablets)
- Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride): potassium supplements and potassium-containing salt substitutes
- medicines for the treatment of diabetes (insulin or tablets) to lower blood sugar
- lithium for treatment of mania or depression
- medicines for the treatment of mental disorders such as depression, anxiety, schizophrenia or other psychoses.
- allopurinol used for the treatment of gout
- immunosuppressants used for the treatment of autoimmune disorders (e.g. rheumatoid arthritis) or following transplant surgery
- procainamide, a treatment for irregular heartbeat
- non-steroidal anti-inflammatory drugs (NSAIDs) medications for pain relief, including aspirin (if dose is higher or equal to 3g/day)
- medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline)
- vasodilators including nitrates (a product that make the blood vessels become wider)
- heparin (blood thinning medication)

Ask your doctor if you are not sure what these medicines are.

Tell your doctor or dentist before having an anaesthetic or surgery because your blood pressure may fall suddenly during the anaesthesia.

Taking Pritnox 2&4 mg with food and drink

It is recommended that Pritnox 2&4 mg to be taken before a meal with sufficient amount of fluid (e.g. water) in order to reduce the influence of food on the way which the medicine works.

Potassium containing food additives or salt substitutes should not be used if you use Pritnox 2&4 mg. The blood potassium concentration can be elevated too high. Also large amounts of (plain) salt (NaCl) in the diet may reduce the antihypertensive effect of Pritnox 2&4 mg.

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 before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril. Perindopril is not recommended in early pregnancy, and must not be taken when 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 is not recommended for 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed.
However, Pritnox 2&4 mg does not affect alertness but different reactions such as dizziness or weakness, in relation to the decrease in blood pressure may occur in certain patients, especially in the beginning of treatment or when increasing the dose. If affected, your ability to drive or to operate machinery may be impaired.

Important information about some of the ingredients of Pritnox 2&4 mg
Pritnox 2&4 mg contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE PRITNOX 2&4 mg

Always take this medicine exactly as your doctor told you. Please ask your doctor or pharmacist if you are not sure.

Pritnox 2&4 mg may be used on its own or with other medicines which lower blood pressure.

The usual dosages for Pritnox 2&4 mg are as follows:

High blood pressure: the usual starting dose is 4 mg once daily in the morning.
In elderly patients, patients with low blood pressure or heart failure, a starting dose of 2 mg can be used.
After a month, this can be increased to 4 mg a day and if necessary to 8 mg a day.

Heart failure: treatment should be under close medical supervision with 2 mg once a day. After two weeks, it can be increased to 4 mg a day if required.

Stable coronary artery disease: the usual starting dose is 4 mg once daily. After two weeks and if 4 mg is well tolerated, this can be increased to 8 mg once daily.
If you are 65 or over, the usual starting dose is 2mg once daily. After one week this can be increased to 4 mg once daily and after a further week to 8 mg once daily.
Your doctor may give you a blood test to check that your
kidneys are working properly before increasing the dose to 8 mg. In case of impaired renal or hepatic function, your doctor will adjust the dose of Pritnox 2&4 mg for you. Take your tablet(s) with a glass of water, preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at the beginning of your treatment with Pritnox 2&4 mg.

Pritnox 2&4 mg is not suitable for use in children

If you take more Pritnox 2&4 mg than you should
If you take too many tablets, contact your nearest hospital casualty department or tell your doctor immediately. The most likely effect in case of an overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

If you forget to take Pritnox 2&4 mg
It is important to take your medicine every day. However, if you forget to take one or more doses, take another as soon as you remember and then go on as prescribed. Do not take a double dose.

If you stop taking Pritnox 2&4 mg
Always consult your doctor, if you wish to stop taking this medicine. Even if you feel well, it may be necessary to continue taking this medicine.

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

4. POSSIBLE SIDE EFFECTS

>Like all medicines, this medicine can cause side effects, although not everybody gets them.

This side effect occurs uncommonly (affecting less than 1 in every 100 people). However, if you notice any of the following side effects, contact your doctor immediately:
- Swelling of the face, lips, mouth, tongue or throat
- Difficulty in breathing
- Dizziness or fainting
- Unusually fast or irregular heart beat
These are symptoms of a serious reaction (angioedema) which can occur with all other drugs of this type (ACE inhibitors). It must be treated immediately, usually in hospital.

Other possible side effects
Common (affecting less than 1 in every 10 people):
- cough, shortness of breath
- light-headness due to low blood pressure (particularly after the first few doses, if the dose is increased or when water tablets are also taken)
- headache, dizziness, vertigo, tiredness, pins and needles, muscle, cramps, visual disturbances (e.g. blurred vision, eye pain), tinnitus (sensation of noises in the ears)
- nausea, vomiting, abdominal pain, changes in your sense of taste, feeling of indigestion, diarrhoea, constipation
- skin rashes, itching
- feeling week
Uncommon (affecting less than 1 in every 100 people):
- changes in mood or sleep
- bronchospasm (tightening of the chest, wheezing and shortness of breath)
- dry mouth
- kidney problems
- impotence
- sweating

Very rare (affecting less than 1 in every 10,000 people):
- confusion
- irregular heart beat, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
- angina pectoris (chest tightness)
- eosinophilic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose)
- pancreatitis (inflammation of the pancreas)
- erythema multiforme (skin reaction disorder resulting from allergic reaction provoked by many different causes)
- acute kidney problems
- changes in the blood cell count: your doctor may decide to carry out blood tests at intervals to monitor for this.

Not known (cannot be estimated from the available data):
- hypoglycaemia (lowering of blood sugar)
- inflammation of blood vessels, often with skin rash

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

5. HOW TO STORE PRITNOX 2&4 mg

Keep out of the reach and sight of children

Do not use Pritnox 2&4 mg after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

Do not store above 25 °C.
Store in the original package in order to protect from light.

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 Pritnox 2&4 mg contains:**
The active substance is: perindopril tert-butyamine.

- **Pritnox 2 mg Tablets:**
  Each tablet contains, 2 mg perindopril tert-butyamine, equivalent to 1.773 mg perindopril as sodium salt (formed in situ) and equivalent to 1.669 mg of perindopril.

- **Pritnox 4 mg Tablets:**
  Each tablet contains, 4 mg perindopril tert-butyamine, equivalent to 3.546mg perindopril as sodium salt (formed in situ) and equivalent to 3.338mg of perindopril.

The other ingredients are: Microcrystalline cellulose, magnesium stearate, lactose anhydrous, maize starch and talc

**What Pritnox 2&4 mg looks like and contents of the pack**

- **2 mg:** White to creamy white, oblong tablets with a score line on each side. An imprint “2” is located on one side of the score line and on each face of the tablet. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

- **4 mg:** White to creamy, oblong tablets with a score line on each side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Aluminium/Aluminium blister.

Pack sizes:
10 tablets
30 tablets
60 tablets
90 tablets

<10mm:

Not all pack sizes may be marketed.

**Marketing authorization holder and Manufacturer**

**MAH**
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

**Manufacturer**
Weimer Pharma GmbH
Im Steingerüst 30, 76437 Rastatt
Germany

&
Galex d.d.
Ti inska ulica 29g
9000 Murska Sobota
Slovenia

This leaflet was last approved in 07/2010.
Pritnox 8 mg, tablets
Perindopril tert-butylamine

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 Pritnox 8 mg is and what it is used for
2. Before you take Pritnox 8 mg
3. How to take Pritnox 8 mg
4. Possible side effects
5. How to store Pritnox 8 mg
6. Further information

1. WHAT PRITNOX 8 mg IS AND WHAT IT IS USED FOR

Pritnox 8 mg belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Pritnox 8 mg tablets are used:
- to treat high blood pressure (hypertension)
To reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

2. BEFORE YOU TAKE PRITNOX 8 mg

Do not take Pritnox 8 mg
- if you are allergic (hypersensitive) to Perindopril or any of the other ingredients in the tablet or any other ACE inhibitor (see section 6).
- if you have had symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, fainting or dizziness with previous ACE inhibitor treatment or have had these symptoms in any other circumstances (this is a condition called angioedema).
- if you have hereditary tendency to tissue swelling or tissue swelling of unknown origin (hereditary or idiopathic angioedema).
- if you are more than 3 months pregnant. (It is also better to avoid Pritnox 8 mg in early pregnancy – see pregnancy section.)

If you think any of the above situations applies to you do not take the tablets. Consult your doctor and take his/her advice.
Take special care with Pritnox 8 mg
You should check with your doctor BEFORE taking Pritnox 8 mg if you:

- are in risk of an excessive fall in the blood pressure. This may be the case, among others, if you suffer from heart failure, impaired renal function of disorders in the salt and fluid balance, e.g. because you take diuretics (medicines that increase urine production) or keep low-salt diet or as a consequence of vomiting or diarrhoea.
- have aortic stenosis (narrowing of the main blood vessel leading from the heart), mitral valve stenosis (narrowing of heart's mitral valve), hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood).
- have hypersensitivity reactions or tissue swelling (angioedema) during treatment with Pritnox 8 mg or other ACE inhibitors.
- Angioneurotic oedema more frequently occur in patients with black skin colour than in patients with non-black skin colour.
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
- are undergoing LDL-apheresis (which is removal of cholesterol from your blood by a machine)
- have a heart problem.
- have a liver problem.
- have a kidney problem, or have recently had a kidney transplantation
- are receiving dialysis.
- suffer from a collagen disease such as systemic lupus erythematosus or sclerodema.
- are on a salt restricted diet or use salt substitutes which contain potassium.
- suffer from a diabetes which is not well controlled
- you must tell your doctor if you think you are (or might become) pregnant. Pritnox 8 mg is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).
- are breast-feeding.

Pritnox 8 mg tablets are not recommended for children.

You should also inform your doctor or medical staff that you are taking Pritnox 8 mg
- if you had an episode of chest pains (angina pectoris).
- if you are to undergo anaesthesia and/or surgery.
- if you have suffered from recent diarrhoea or vomiting.
- If your blood pressure is not sufficiently lowered due to your ethnic affiliation (particularly in patients with black skin colour).
- If you have a persistent dry cough.
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, herbal or natural products. In particular, you should check with your doctor if you are taking any of the following to be sure that it is safe to take Pritnox 8 mg:

- Other medicines for treating high blood pressure including diuretics (water tablets)
- Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride): potassium supplements and potassium-containing salt substitutes
- medicines for the treatment of diabetes (insulin or tablets) to lower blood sugar
- lithium for treatment of mania or depression
- medicines for the treatment of mental disorders such as depression, anxiety, schizophrenia or other psychoses.
- allopurinol used for the treatment of gout
- immunosuppressants used for the treatment of autoimmune disorders (e.g. rheumatoid arthritis) or following transplant surgery
- procainamide, a treatment for irregular heartbeat
- non-steroidal anti-inflammatory drugs (NSAIDs) medications for pain relief, including aspirin (if dose is higher or equal to 3g/day)
- medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline)
- vasodilators including nitrates (a product that make the blood vessels become wider)
- heparin (blood thinning medication)

Ask your doctor if you are not sure what these medicines are.

Tell your doctor or dentist before having an anaesthetic or surgery because your blood pressure may fall suddenly during the anaesthesia.

Taking Pritnox 8 mg with food and drink
It is recommended that Pritnox 8 mg to be taken before a meal with sufficient amount of fluid (e.g. water) in order to reduce the influence of food on the way which the medicine works. Potassium containing food additives or salt substitutes should not be used if you use Pritnox 8 mg. The blood potassium concentration can be elevated too high. Also large amounts of (plain) salt (NaCl) in the diet may reduce the antihypertensive effect of Pritnox 8 mg.

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 before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril. Perindopril is not recommended in early pregnancy, and must not be taken when 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 is not recommended for 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. However, Pritnox 8 mg does not affect alertness but different reactions such as dizziness or weakness, in relation to the decrease in blood pressure may occur in certain patients, especially in the beginning of treatment or when increasing the dose. If affected, your ability to drive or to operate machinery may be impaired.

Important information about some of the ingredients of Pritnox 8 mg
Pritnox 8 mg contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE PRITNOX 8 mg

Always take this medicine exactly as your doctor told you. Please ask your doctor or pharmacist if you are not sure.

Pritnox 8 mg may be used on its own or with other medicines which lower blood pressure. Not all mentioned posologies are possible with the product in this Leaflet.

The usual dosages for Pritnox 8 mg are as follows:
**High blood pressure:** the usual starting dose is 4 mg once daily in the morning.
In elderly patients, patients with low blood pressure or heart failure, a starting dose of 2 mg can be used.
After a month, this can be increased to 4 mg a day and if necessary to 8 mg a day.

**Stable coronary artery disease:** the usual starting dose is 4 mg once daily. After two weeks and if 4 mg is well tolerated, this can be increased to 8 mg once daily.
If you are 65 or over, the usual starting dose is 2mg once daily. After one week this can be increased to 4 mg once daily and after a further week to 8 mg once daily.
Your doctor may give you a blood test to check that your
kidneys are working properly before increasing the dose to 8 mg.  
In case of impaired renal or hepatic function, your doctor will adjust the dose of Pritnox 8 mg for you. 
Take your tablet(s) with a glass of water, preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at the beginning of your treatment with Pritnox 8 mg.

Pritnox 8 mg is not suitable for use in children

**If you take more Pritnox 8 mg than you should**
If you take too many tablets, contact your nearest hospital casualty department or tell your doctor immediately. The most likely effect in case of an overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

**If you forget to take Pritnox 8 mg**
It is important to take your medicine every day. However, if you forget to take one or more doses, take another as soon as you remember and then go on as prescribed. Do not take a double dose.

**If you stop taking Pritnox 8 mg**
Always consult your doctor, if you wish to stop taking this medicine. Even if you feel well, it may be necessary to continue taking this medicine.

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

**4. POSSIBLE SIDE EFFECTS**

*Like all medicines, this medicine can cause side effects, although not everybody gets them.*

This side effect occurs uncommonly (affecting less than 1 in every 100 people). However, if you notice any of the following side effects, contact your doctor immediately:
- Swelling of the face, lips, mouth, tongue or throat
- Difficulty in breathing
- Dizziness or fainting
- Unusually fast or irregular heart beat

These are symptoms of a serious reaction (angioedema) which can occur with all other drugs of this type (ACE inhibitors). It must be treated immediately, usually in hospital.
Other possible side effects

**Common (affecting less than 1 in every 10 people):**
- cough, shortness of breath
- light-headedness due to low blood pressure (particularly after the first few doses, if the dose is increased or when water tablets are also taken)
- headache, dizziness, vertigo, tiredness, pins and needles, muscle, cramps, visual disturbances (e.g. blurred vision, eye pain), tinnitus (sensation of noises in the ears)
- nausea, vomiting, abdominal pain, changes in your sense of taste, feeling of indigestion, diarrhoea, constipation
- skin rashes, itching
- feeling week

**Uncommon (affecting less than 1 in every 100 people):**
- changes in mood or sleep
- bronchospasm (tightening of the chest, wheezing and shortness of breath)
- dry mouth
- kidney problems
- impotence
- sweating

**Very rare (affecting less than 1 in every 10,000 people):**
- confusion
- irregular heart beat, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
- angina pectoris (chest tightness)
- eosinophilic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose)
- pancreatitis (inflammation of the pancreas)
- erythema multiforme (skin reaction disorder resulting from allergic reaction provoked by many different causes)
- acute kidney problems
- changes in the blood cell count; your doctor may decide to carry out blood tests at intervals to monitor for this.

**Not known (cannot be estimated from the available data):**
- hypoglycaemia (lowering of blood sugar)
- inflammation of blood vessels, often with skin rash

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

5. **HOW TO STORE PRITNOX 8 mg**

Keep out of the reach and sight of children

Do not use Pritnox 8 mg after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

Do not store above 25°C.
Store in the original package in order to protect from light.

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 Pritnox 8 mg contains:
The active substance is: perindopril tert-butylamine.

Each tablet contains, 8 mg perindopril tert-butylamine, equivalent to 7.092mg perindopril as sodium salt (formed in situ) and equivalent to 6.676 mg of perindopril.

The other ingredients are: Microcrystalline cellulose, magnesium stearate, lactose anhydrous, maize starch and talc

What Pritnox 8 mg looks like and contents of the pack

White to creamy, round, biconvex tablets.

Aluminium/Aluminium blister.

Pack sizes:
10 tablets
30 tablets
60 tablets
90 tablets
Not all pack sizes may be marketed.

Marketing authorization holder and Manufacturer

MAH
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

Manufacturer
Weimer Pharma GmbH
Im Steingerüst 30, 76437 Rastatt
Germany
&
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

This leaflet was last approved in 07/2010.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Peryl 2&4 mg, tablets
Perindopril tert-butylamine

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 Peryl 2&4 mg is and what it is used for
2. Before you take Peryl 2&4 mg
3. How to take Peryl 2&4 mg
4. Possible side effects
5. How to store Peryl 2&4 mg
6. Further information

1. WHAT PERYL 2&4 mg IS AND WHAT IT IS USED FOR

Peryl 2&4 mg belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Peryl 2&4 mg tablets are used:
- to treat high blood pressure (hypertension)
- to treat heart failure (a condition where the heart is unable to pump enough to meet the body’s needs).
- To reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

2. BEFORE YOU TAKE PERYL 2&4 mg

Do not take Peryl 2&4 mg
- if you are allergic (hypersensitive) to Perindopril or any of the other ingredients in the tablet or any other ACE inhibitor (see section 6).
- if you have had symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, fainting or dizziness with previous ACE inhibitor treatment or have had these symptoms in any other circumstances (this is a condition called angioedema).
- if you have hereditary tendency to tissue swelling or tissue swelling of unknown origin (hereditary or idiopathic angioedema).
- if you are more than 3 months pregnant. (It is also better to avoid Peryl 2&4 mg in early pregnancy – see pregnancy section.)

If you think any of the above situations applies to you do not take the tablets. Consult your doctor and take his/her advice.
Take special care with Peryl 2&4 mg
You should check with your doctor BEFORE taking Peryl 2&4 mg if you:

- are in risk of an excessive fall in the blood pressure. This may be the case, among others, if you suffer from heart failure, impaired renal function of disorders in the salt and fluid balance, e.g. because you take diuretics (medicines that increase urine production) or keep low-salt diet or as a consequence of vomiting or diarrhoea.
- have aortic stenosis (narrowing of the main blood vessel leading from the heart), mitral valv stenosis (narrowing of heart’s mitral valve), hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood).
- have hypersensitivity reactions or tissue swelling (angioedema) during treatment with Peryl 2&4 mg or other ACE inhibitors.
- Angioneurotic oedema more frequently occur in patients with black skin colour than in patients with non-black skin colour.
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
- are undergoing LDL-apheresis (which is removal of cholesterol from your blood by a machine)
- have a heart problem.
- have a liver problem.
- have a kidney problem, or have recently had a kidney transplantation
- are receiving dialysis.
- suffer from a collagen disease such as systemic lupus erythematosus or sclerodema.
- are on a salt restricted diet or use salt substitutes which contain potassium.
- suffer from a diabetes which is not well controlled
- you must tell your doctor if you think you are (or might become) pregnant. Peryl 2&4 mg is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).
- are breast-feeding.

Peryl 2&4 mg tablets are not recommended for children.

You should also inform your doctor or medical staff that you are taking Peryl 2&4 mg
- if you had an episode of chest pains (angina pectoris).
- if you are to undergo anaesthesia and/or surgery.
- if you have suffered from recent diarrhoea or vomiting.
- If your blood pressure is not sufficiently lowered due to your ethnic affiliation (particularly in patients with black skin colour).
- If you have a persistent dry cough.
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, herbal or natural products. In particular, you should check with your doctor if you are taking any of the following to be sure that it is safe to take Peryl 2&4 mg:

- Other medicines for treating high blood pressure including diuretics (water tablets)
- Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride): potassium supplements and potassium-containing salt substitutes
- Medicines for the treatment of diabetes (insulin or tablets) to lower blood sugar
- Lithium for treatment of mania or depression
- Medicines for the treatment of mental disorders such as depression, anxiety, schizophrenia or other psychoses.
- Allopurinol used for the treatment of gout
- Immunosuppressants used for the treatment of autoimmune disorders (e.g. rheumatoid arthritis) or following transplant surgery
- Procanamide, a treatment for irregular heartbeat
- Non-steroidal anti-inflammatory drugs (NSAIDs) medications for pain relief, including aspirin (if dose is higher or equal to 3g/day)
- Medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline)
- Vasodilators including nitrates (a product that make the blood vessels become wider)
- Heparin (blood thinning medication)

Ask your doctor if you are not sure what these medicines are.

Tell your doctor or dentist before having an anaesthetic or surgery because your blood pressure may fall suddenly during the anaesthesia.

Taking Peryl 2&4 mg with food and drink

It is recommended that Peryl 2&4 mg to be taken before a meal with sufficient amount of fluid (e.g. water) in order to reduce the influence of food on the way which the medicine works.

Potassium containing food additives or salt substitutes should not be used if you use Peryl 2&4 mg. The blood potassium concentration can be elevated too high. Also large amounts of (plain) salt (NaCl) in the diet may reduce the antihypertensive effect of Peryl 2&4 mg.

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 before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril. Perindopril is not recommended in early pregnancy, and must not be taken when 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 is not recommended for 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. However, Peryl 2&4 mg does not affect alertness but different reactions such as dizziness or weakness, in relation to the decrease in blood pressure may occur in certain patients, especially in the beginning of treatment or when increasing the dose. If affected, your ability to drive or to operate machinery may be impaired.

Important information about some of the ingredients of Peryl 2&4 mg
Peryl 2&4 mg contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE PERYL 2&4 mg
Always take this medicine exactly as your doctor told you. Please ask your doctor or pharmacist if you are not sure.

Peryl 2&4 mg may be used on its own or with other medicines which lower blood pressure.

The usual dosages for Peryl 2&4 mg are as follows:
**High blood pressure:** the usual starting dose is 4 mg once daily in the morning.
In elderly patients, patients with low blood pressure or heart failure, a starting dose of 2 mg can be used.
After a month, this can be increased to 4 mg a day and if necessary to 8 mg a day.

**Heart failure:** treatment should be under close medical supervision with 2 mg once a day. After two weeks, it can be increased to 4 mg a day if required.

**Stable coronary artery disease:** the usual starting dose is 4 mg once daily. After two weeks and if 4 mg is well tolerated, this can be increased to 8 mg once daily.
If you are 65 or over, the usual starting dose is 2mg once daily. After one week this can be increased to 4 mg once daily and after a further week to 8 mg once daily.
Your doctor may give you a blood test to check that your kidneys are working properly before increasing the dose to 8 mg.

In case of impaired renal or hepatic function, your doctor will adjust the dose of Peryl 2&4 mg for you.
Take your tablet(s) with a glass of water, preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at the beginning of your treatment with Peryl 2&4 mg.

Peryl 2&4 mg is not suitable for use in children

If you take more Peryl 2&4 mg than you should
If you take too many tablets, contact your nearest hospital casualty department or tell your doctor immediately. The most likely effect in case of an overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

If you forget to take Peryl 2&4 mg
It is important to take your medicine every day. However, if you forget to take one or more doses, take another as soon as you remember and then go on as prescribed. Do not take a double dose.

If you stop taking Peryl 2&4 mg
Always consult your doctor, if you wish to stop taking this medicine. Even if you feel well, it may be necessary to continue taking this medicine.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

This side effect occurs uncommonly (affecting less than 1 in every 100 people). However, if you notice any of the following side effects, contact your doctor immediately:
- Swelling of the face, lips, mouth, tongue or throat
- Difficulty in breathing
- Dizziness or fainting
- Unusually fast or irregular heart beat
These are symptoms of a serious reaction (angioedema) which can occur with all other drugs of this type (ACE inhibitors). It must be treated immediately, usually in hospital.

Other possible side effects
Common (affecting less than 1 in every 10 people):
- cough, shortness of breath
- light-headedness due to low blood pressure (particularly after the first few doses, if the dose is increased or when water tablets are also taken)
- headache, dizziness, vertigo, tiredness, pins and needles, muscle, cramps, visual disturbances (e.g. blurred vision, eye pain), tinnitus (sensation of noises in the ears)
- nausea, vomiting, abdominal pain, changes in your sense of taste, feeling of indigestion, diarrhoea, constipation
- skin rashes, itching
- feeling week
Uncommon (affecting less than 1 in every 100 people):
- changes in mood or sleep
- bronchospasm (tightening of the chest, wheezing and shortness of breath)
- dry mouth
- kidney problems
- impotence
- sweating

Very rare (affecting less than 1 in every 10,000 people):
- confusion
- irregular heart beat, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
- angina pectoris (chest tightness)
- eosinophillic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose)
- pancreatitis (inflammation of the pancreas)
- erythema multiforme (skin reaction disorder resulting from allergic reaction provoked by many different causes)
- acute kidney problems
- changes in the blood cell count: your doctor may decide to carry out blood tests at intervals to monitor for this.

Not known (cannot be estimated from the available data):
- hypoglycaemia (lowering of blood sugar)
- inflammation of blood vessels, often with skin rash

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

5. HOW TO STORE PERYL 2&4 mg

Keep out of the reach and sight of children

Do not use Peryl 2&4 mg after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

Do not store above 25 °C.
Store in the original package in order to protect from light.

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 Peryl 2 & 4 mg contains:
The active substance is: perindopril tert-butylamine.

- Peryl 2 mg Tablets:
  Each tablet contains, 2 mg perindopril tert-butylamine, equivalent to 1.773 mg perindopril as sodium salt (formed in situ) and equivalent to 1.669 mg of perindopril.

- Peryl 4 mg Tablets:
  Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.546 mg perindopril as sodium salt (formed in situ) and equivalent to 3.338 mg of perindopril.

The other ingredients are: Microcrystalline cellulose, magnesium stearate, lactose anhydrous, maize starch and talc.

What Peryl 2 & 4 mg looks like and contents of the pack

- 2 mg: White to creamy white, oblong tablets with a score line on each side. An imprint “2” is located on one side of the score line and on each face of the tablet. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

- 4 mg: White to creamy, oblong tablets with a score line on each side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Aluminium/Aluminium blister.

Pack sizes:
30 tablets
60 tablets
90 tablets

Not all pack sizes may be marketed.

Marketing authorization holder and Manufacturer

MAH
Galex d.d.
Tišinska ulica 29g
3000 Murska Sobota
Slovenia

Manufacturer
Weimar Pharma GmbH
Im Steingerüst 30, 76437 Rastatt
Germany
&
Galex d.d.
Tišinska ulica 29g
3000 Murska Sobota
Slovenia
&
ICN Polfa Rzeszów S.A.
2 Przemysłowa Street, 36-959 Rzeszów
Poland

This leaflet was last approved in 07/2010.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Peryl 8 mg, tablets
Perindopril tert-butylamine

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 Peryl 8 mg is and what it is used for
2. Before you take Peryl 8 mg
3. How to take Peryl 8 mg
4. Possible side effects
5. How to store Peryl 8 mg
6. Further information

1. WHAT PERYL 8 mg IS AND WHAT IT IS USED FOR

Peryl 8 mg belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Peryl 8 mg tablets are used:
• to treat high blood pressure (hypertension)
To reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

2. BEFORE YOU TAKE PERYL 8 mg

Do not take Peryl 8 mg
• if you are allergic (hypersensitive) to Perindopril or any of the other ingredients in the tablet or any other ACE inhibitor (see section 6).
• if you have had symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, fainting or dizziness with previous ACE inhibitor treatment or have had these symptoms in any other circumstances (this is a condition called angioedema).
• if you have hereditary tendency to tissue swelling or tissue swelling of unknown origin (hereditary or idiopathic angioedema).
• if you are more than 3 months pregnant. (It is also better to avoid Peryl 8 mg in early pregnancy – see pregnancy section.)

If you think any of the above situations applies to you do not take the tablets. Consult your doctor and take his/her advice.
Take special care with Peryl 8 mg
You should check with your doctor BEFORE taking Peryl 8 mg if you:

• are in risk of an excessive fall in the blood pressure. This may be the case, among others, if you suffer from heart failure, impaired renal function of disorders in the salt and fluid balance, e.g. because you take diuretics (medicines that increase urine production) or keep low-salt diet or as a consequence of vomiting or diarrhoea.
• have aortic stenosis (narrowing of the main blood vessel leading from the heart), mitral valv stenosis (narrowing of heart’s mitral valve), hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood).
• have hypersensitivity reactions or tissue swelling (angioedema) during treatment with Peryl 8 mg or other ACE inhibitors.
• Angioneurotic oedema more frequently occur in patients with black skin colour than in patients with non-black skin colour.
• are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
• are undergoing LDL-apheresis (which is removal of cholesterol from your blood by a machine)
• have a heart problem.
• have a liver problem.
• have a kidney problem, or have recently had a kidney transplantation
• are receiving dialysis.
• suffer from a collagen disease such as systemic lupus erythematosus or sclerodema.
• are on a salt restricted diet or use salt substitutes which contain potassium.
• suffer from a diabetes which is not well controlled
• you must tell your doctor if you think you are (or might become) pregnant. Peryl 8 mg is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).
• are breast-feeding.

Peryl 8 mg tablets are not recommended for children.

You should also inform your doctor or medical staff that you are taking Peryl 8 mg
• if you had an episode of chest pains (angina pectoris).
• if you are to undergo anaesthesia and/or surgery.
• if you have suffered from recent diarrhoea or vomiting.
• If your blood pressure is not sufficiently lowered due to your ethnic affiliation (particularly in patients with black skin colour).
• If you have a persistent dry cough.
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, herbal or natural products. In particular, you should check with your doctor if you are taking any of the following to be sure that it is safe to take Peryl 8 mg:

- Other medicines for treating high blood pressure including diuretics (water tablets)
- Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride): potassium supplements and potassium-containing salt substitutes
- medicines for the treatment of diabetes (insulin or tablets) to lower blood sugar
- lithium for treatment of mania or depression
- medicines for the treatment of mental disorders such as depression, anxiety, schizophrenia or other psychoses.
- allopurinol used for the treatment of gout
- immunosuppressants used for the treatment of auto-immune disorders (e.g. rheumatoid arthritis) or following transplant surgery
- procainamide, a treatment for irregular heartbeat
- non-steroidal anti-inflammatory drugs (NSAIDs) medications for pain relief, including aspirin (if dose is higher or equal to 3g/day)
- medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline)
- vasodilators including nitrates (a product that make the blood vessels become wider)
- heparin (blood thinning medication)

Ask your doctor if you are not sure what these medicines are.

Tell your doctor or dentist before having an anaesthetic or surgery because your blood pressure may fall suddenly during the anaesthesia.

Taking Peryl 8 mg with food and drink

It is recommended that Peryl 8 mg to be taken before a meal with sufficient amount of fluid (e.g. water) in order to reduce the influence of food on the way which the medicine works.

Potassium containing food additives or salt substitutes should not be used if you use Peryl 8 mg. The blood potassium concentration can be elevated too high. Also large amounts of (plain) salt (NaCl) in the diet may reduce the antihypertensive effect of Peryl 8 mg.

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 before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril. Perindopril is not recommended in early pregnancy, and must not be taken when 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 is not recommended for 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. However, Peryl 8 mg does not affect alertness but different reactions such as dizziness or weakness, in relation to the decrease in blood pressure may occur in certain patients, especially in the beginning of treatment or when increasing the dose. If affected, your ability to drive or to operate machinery may be impaired.

Important information about some of the ingredients of Peryl 8 mg
Peryl 8 mg contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE PERYL 8 mg

Always take this medicine exactly as your doctor told you. Please ask your doctor or pharmacist if you are not sure.

Peryl 8 mg may be used on its own or with other medicines which lower blood pressure. Not all mentioned posologies are possible with the product in this Leaflet.

The usual dosages for Peryl 8 mg are as follows:
High blood pressure: the usual starting dose is 4 mg once daily in the morning. In elderly patients, patients with low blood pressure or heart failure, a starting dose of 2 mg can be used. After a month, this can be increased to 4 mg a day and if necessary to 8 mg a day.

Stable coronary artery disease: the usual starting dose is 4 mg once daily. After two weeks and if 4 mg is well tolerated, this can be increased to 8 mg once daily. If you are 65 or over, the usual starting dose is 2mg once daily. After one week this can be increased to 4 mg once daily and after a further week to 8 mg once daily. Your doctor may give you a blood test to check that your
kidneys are working properly before increasing the dose to 8 mg.
In case of impaired renal or hepatic function, your doctor will adjust the dose of Peryl 8 mg for you.
Take your tablet(s) with a glass of water, preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at the beginning of your treatment with Peryl 8 mg.

Peryl 8 mg is not suitable for use in children

If you take more Peryl 8 mg than you should
If you take too many tablets, contact your nearest hospital casualty department or tell your doctor immediately. The most likely effect in case of an overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

If you forget to take Peryl 8 mg
It is important to take your medicine every day. However, if you forget to take one or more doses, take another as soon as you remember and then go on as prescribed. Do not take a double dose.

If you stop taking Peryl 8 mg
Always consult your doctor, if you wish to stop taking this medicine. Even if you feel well, it may be necessary to continue taking this medicine.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

This side effect occurs uncommonly (affecting less than 1 in every 100 people). However, if you notice any of the following side effects, contact your doctor immediately:
- Swelling of the face, lips, mouth, tongue or throat
- Difficulty in breathing
- Dizziness or fainting
- Unusually fast or irregular heart beat
These are symptoms of a serious reaction (angioedema) which can occur with all other drugs of this type (ACE inhibitors). It must be treated immediately, usually in hospital.

Other possible side effects
Common (affecting less than 1 in every 10 people):
- cough, shortness of breath
- light-headedness due to low blood pressure (particularly after the first few doses, if the dose is increased or when water tablets are also taken)
- headache, dizziness, vertigo, tiredness, pins and needles, muscle, cramps, visual disturbances (e.g. blurred vision, eye pain), tinnitus (sensation of noises in the ears)
- nausea, vomiting, abdominal pain, changes in your sense of taste, feeling of indigestion, diarrhoea, constipation
- skin rashes, itching
- feeling week
Uncommon (affecting less than 1 in every 100 people):
• changes in mood or sleep
• bronchospasm (tightening of the chest, wheezing and shortness of breath)
• dry mouth
• kidney problems
• impotence
• sweating

Very rare (affecting less than 1 in every 10,000 people):
• confusion
• irregular heart beat, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
• angina pectoris (chest tightness)
• eosinophilic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose)
• pancreatitis (inflammation of the pancreas)
• erythema multiforme (skin reaction disorder resulting from allergic reaction provoked by many different causes)
• acute kidney problems
• changes in the blood cell count: your doctor may decide to carry out blood tests at intervals to monitor for this.

Not known (cannot be estimated from the available data):
• hypoglycaemia (lowering of blood sugar)
• inflammation of blood vessels, often with skin rash

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

5. HOW TO STORE PERYL 8 mg

Keep out of the reach and sight of children

Do not use Peryl 8 mg after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

Do not store above 25°C.
Store in the original package in order to protect from light.

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 Peryl 8 mg contains:
The active substance is: perindopril tert-butylamine.

Each tablet contains, 8 mg perindopril tert-butylamine, equivalent to 7.092mg perindopril as sodium salt (formed in situ) and equivalent to 6.676 mg of perindopril.

The other ingredients are: Microcrystalline cellulose, magnesium stearate, lactose anhydrous, maize starch and talc.

What Peryl 8 mg looks like and contents of the pack

White to creamy, round, biconvex tablets.

Aluminium/Aluminium blister.

Pack sizes:
30 tablets
60 tablets
90 tablets

Not all pack sizes may be marketed.

Marketing authorization holder and Manufacturer

MAH
Galex d.d.
Tilšinska ulica 29g
9000 Murska Sobota
Slovenia

Manufacturer
Weimer Pharma GmbH
Im Steingerüst 30, 76437 Rastatt
Germany
&
Galex d.d.
Tilšinska ulica 29g
9000 Murska Sobota
Slovenia
&
ICN Polfa Rzeszów S.A.
2 Przemysłowa Street, 35-959 Rzeszów
Poland

This leaflet was last approved in 07/2010.
PAR Pritnox and Perilex 2, 4 and 8mg Tablets and Peryl 4 and 8mg Tablets

UK/H/1625/001-3/DC, UK/H/3097/001-3/DC and
UK/H/3119/001-2/DC

PACKAGE LEAFLET: INFORMATION FOR THE USER

Perilex 4 mg, tablets
Perindopril tert-butylamine

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 Perilex 4 mg is and what it is used for
2. Before you take Perilex 4 mg
3. How to take Perilex 4 mg
4. Possible side effects
5. How to store Perilex 4 mg
6. Further information

1. WHAT PERILEX 4 mg IS AND WHAT IT IS USED FOR

Perilex 4 mg belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Perilex 4 mg tablets are used:
- to treat high blood pressure (hypertension)
- to treat heart failure (a condition where the heart is unable to pump enough to meet the body’s needs)
- To reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

2. BEFORE YOU TAKE PERILEX 4 mg

Do not take Perilex 4 mg
- if you are allergic (hypersensitive) to Perindopril or any of the other ingredients in the tablet or any other ACE inhibitor (see section 6).
- if you have had symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, tainting or dizziness with previous ACE inhibitor treatment or have had these symptoms in any other circumstances (this is a condition called angioedema).
- if you have hereditary tendency to tissue swelling or tissue swelling of unknown origin (hereditary or idiopathic angioedema).
- if you are more than 3 months pregnant. (It is also better to avoid Perilex 4 mg in early pregnancy – see pregnancy section.)

If you think any of the above situations applies to you do not take the tablets. Consult your doctor and take his/her advice.
Take special care with Perilex 4 mg
You should check with your doctor BEFORE taking Perilex 4 mg if you:

- are in risk of an excessive fall in the blood pressure. This may be the case, among others, if you suffer from heart failure, impaired renal function of disorders in the salt and fluid balance, e.g. because you take diuretics (medicines that increase urine production) or keep low-salt diet or as a consequence of vomiting or diarrhoea.
- have aortic stenosis (narrowing of the main blood vessel leading from the heart), mitral valve stenosis (narrowing of heart's mitral valve), hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood).
- have hypersensitivity reactions or tissue swelling (angioedema) during treatment with Perilex 4 mg or other ACE inhibitors.
- Angioneurotic oedema more frequently occur in patients with black skin colour than in patients with non-black skin colour.
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
- are undergoing LDL-apheresis (which is removal of cholesterol from your blood by a machine)
- have a heart problem.
- have a liver problem.
- have a kidney problem, or have recently had a kidney transplantation.
- are receiving dialysis.
- suffer from a collagen disease such as systemic lupus erythematosus or scleroderma.
- are on a salt restricted diet or use salt substitutes which contain potassium.
- suffer from a diabetes which is not well controlled
- you must tell your doctor if you think you are (or might become) pregnant. Perilex 4 mg is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).
- are breast-feeding.

Perilex 4 mg tablets are not recommended for children.

You should also inform your doctor or medical staff that you are taking Perilex 4 mg
- if you had an episode of chest pains (angina pectoris).
- if you are to undergo anaesthesia and/or surgery.
- if you have suffered from recent diarrhoea or vomiting.
- If your blood pressure is not sufficiently lowered due to your ethnic affiliation (particularly in patients with black skin colour).
- if you have a persistent dry cough.
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, herbal or natural products. In particular, you should check with your doctor if you are taking any of the following to be sure that it is safe to take Perilex 4 mg:

- Other medicines for treating high blood pressure including diuretics (water tablets)
- Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride): potassium supplements and potassium-containing salt substitutes
- Medicines for the treatment of diabetes (insulin or tablets) to lower blood sugar
- Lithium for treatment of mania or depression
- Medicines for the treatment of mental disorders such as depression, anxiety, schizophrenia or other psychoses.
- Allopurinol used for the treatment of gout
- Immunosuppressants used for the treatment of autoimmune disorders (e.g. rheumatoid arthritis) or following transplant surgery
- Procainamide, a treatment for irregular heartbeat
- Non-steroidal anti-inflammatory drugs (NSAIDs) medications for pain relief, including aspirin (if dose is higher or equal to 3g/day)
- Medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline)
- Vasodilators including nitrates (a product that makes the blood vessels become wider)
- Heparin (blood thinning medication)

Ask your doctor if you are not sure what these medicines are.

Tell your doctor or dentist before having an anaesthetic or surgery because your blood pressure may fall suddenly during the anaesthesia.

Taking Perilex 4 mg with food and drink

It is recommended that Perilex 4 mg be taken before a meal with sufficient amount of fluid (e.g. water) in order to reduce the influence of food on the way which the medicine works.

Potassium containing food additives or salt substitutes should not be used if you use Perilex 4 mg. The blood potassium concentration can be elevated too high. Also large amounts of (plain) salt (NaCl) in the diet may reduce the antihypertensive effect of Perilex 4 mg.

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 before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril. Perindopril is not recommended in early pregnancy, and must not be taken when 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 is not recommended for 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. However, Perilex 4 mg does not affect alertness but different reactions such as dizziness or weakness, in relation to the decrease in blood pressure may occur in certain patients, especially in the beginning of treatment or when increasing the dose. If affected, your ability to drive or to operate machinery may be impaired.

Important information about some of the ingredients of Perilex 4 mg
Perilex 4 mg contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE PERILEX 4 mg
Always take this medicine exactly as your doctor told you. Please ask your doctor or pharmacist if you are not sure.

Perilex 4 mg may be used on its own or with other medicines which lower blood pressure.

The usual dosages for Perilex 4 mg are as follows:
High blood pressure: the usual starting dose is 4 mg once daily in the morning.
In elderly patients, patients with low blood pressure or heart failure, a starting dose of 2 mg can be used.
After a month, this can be increased to 4 mg a day and if necessary to 8 mg a day.

Heart failure: treatment should be under close medical supervision with 2 mg once a day. After two weeks, it can be increased to 4 mg a day if required.

Stable coronary artery disease: the usual starting dose is 4 mg once daily. After two weeks and if 4 mg is well tolerated, this can be increased to 8 mg once daily.
If you are 65 or over, the usual starting dose is 2 mg once daily. After one week this can be increased to 4 mg once daily and after a further week to 8 mg once daily.
Your doctor may give you a blood test to check that your kidneys are working properly before increasing the dose to 8 mg.

In case of impaired renal or hepatic function, your doctor will adjust the dose of Perilex 4 mg for you.

Take your tablet(s) with a glass of water, preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at the beginning of your treatment with Perilex 4 mg.

Perilex 4 mg is not suitable for use in children.

If you take more Perilex 4 mg than you should:
If you take too many tablets, contact your nearest hospital casualty department or tell your doctor immediately. The most likely effect in case of an overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

If you forget to take Perilex 4 mg:
It is important to take your medicine every day. However, if you forget to take one or more doses, take another as soon as you remember and then go on as prescribed. Do not take a double dose.

If you stop taking Perilex 4 mg:
Always consult your doctor, if you wish to stop taking this medicine. Even if you feel well, it may be necessary to continue taking this medicine.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

This side effect occurs uncommonly (affecting less than 1 in every 100 people). However, if you notice any of the following side effects, contact your doctor immediately:
- Swelling of the face, lips, mouth, tongue or throat
- Difficulty in breathing
- Dizziness or fainting
- Unusually fast or irregular heart beat
These are symptoms of a serious reaction (angioedema) which can occur with all other drugs of this type (ACE inhibitors). It must be treated immediately, usually in hospital.

Other possible side effects
Common (affecting less than 1 in every 10 people):
- Cough, shortness of breath
- Light-headedness due to low blood pressure (particularly after the first few doses, if the dose is increased or when water tablets are also taken)
- Headache, dizziness, dizziness, tiredness, pins and needles, muscle cramps, visual disturbances (e.g. blurred vision, eye pain), tinnitus (sensation of noises in the ears)
- Nausea, vomiting, abdominal pain, changes in your sense of taste, feeling of indigestion, diarrhoea, constipation
- Skin rashes, itching
- Feeling week
Uncommon (affecting less than 1 in every 100 people):
- changes in mood or sleep
- bronchospasm (tightening of the chest, wheezing and shortness of breath)
- dry mouth
- kidney problems
- impotence
- sweating

Very rare (affecting less than 1 in every 10,000 people):
- confusion
- irregular heart beat, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
- angina pectoris (chest tightness)
- eosinophilic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose)
- pancreatitis (inflammation of the pancreas)
- erythema multiforme (skin reaction disorder resulting from allergic reaction provoked by many different causes)
- acute kidney problems
- changes in the blood cell count: your doctor may decide to carry out blood tests at intervals to monitor for this.

Not known (cannot be estimated from the available data):
- hypoglycaemia (lowering of blood sugar)
- inflammation of blood vessels, often with skin rash

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

5. HOW TO STORE PERILEX 4 mg

Keep out of the reach and sight of children

Do not use Perilex 4 mg after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

Do not store above 25 °C.
Store in the original package in order to protect from light.

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 Perilex 4 mg contains:**
The active substance is: perindopril tert-butylamine.

- **Perilex 2 mg Tablets:**
  Each tablet contains, 2 mg perindopril tert-butylamine, equivalent to 1.773 mg perindopril as sodium salt (formed in situ) and equivalent to 1.669 mg of perindopril.
- **Perilex 4 mg Tablets:**
  Each tablet contains, 4 mg perindopril tert-butylamine, equivalent to 3.548 mg perindopril as sodium salt (formed in situ) and equivalent to 3.338 mg of perindopril.

The other ingredients are: Microcrystalline cellulose, magnesium stearate, lactose anhydrous, maize starch and talc.

**What Perilex 4 mg looks like and contents of the pack**

- **2 mg:** White to creamy white, oblong tablets with a score line on each side. An imprint “2” is located on one side of the score line and on each face of the tablet. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

- **4mg:** White to creamy, oblong tablets with a score line on each side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

*Aluminium/Aluminium blister.*

**Pack sizes:**
- 30 tablets
- 60 tablets
- 90 tablets

Not all pack sizes may be marketed.

**Marketing authorization holder and Manufacturer**

**MAH**
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

**Manufacturer**
Weimer Pharma GmbH
Im Steingerust 30, 76437 Rastatt
Germany
&
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia
&
PNG GEROLYMATOS S.A. (PLANT B)
4, Asklipioi str., 14568 Kryoneri Attiki
Greece

This leaflet was last approved in 07/2010.
PACKAGE LEAFLET: INFORMATION FOR THE USER

Perilex 8 mg, tablets
Perindopril tert-butyramine

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:
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6. Further information

1. WHAT PERILEX 8 mg IS AND WHAT IT IS USED FOR

Perilex 8 mg belongs to a class of medicines called ACE inhibitors. These work by widening the blood vessels, which makes it easier for your heart to pump blood through them.

Perilex 8 mg tablets are used:
- to treat high blood pressure (hypertension)
To reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

2. BEFORE YOU TAKE PERILEX 8 mg

Do not take Perilex 8 mg
• if you are allergic (hypersensitive) to Perindopril or any of the other ingredients in the tablet or any other ACE inhibitor (see section 6).
• if you have had symptoms such as wheezing, swelling of the face, tongue or throat, intense itching, skin rashes, fainting or dizziness with previous ACE inhibitor treatment or have had these symptoms in any other circumstances (this is a condition called angioedema).
• if you have hereditary tendency to tissue swelling or tissue swelling of unknown origin (hereditary or idiopathic angioedema).
• if you are more than 3 months pregnant. (It is also better to avoid Perilex 8 mg in early pregnancy – see pregnancy section.)

If you think any of the above situations applies to you do not take the tablets. Consult your doctor and take his/her advice.
Take special care with Perilex 8 mg
You should check with your doctor BEFORE taking Perilex 8 mg if you:

- are in risk of an excessive fall in the blood pressure. This may be the case, among others, if you suffer from heart failure, impaired renal function of disorders in the salt and fluid balance, e.g. because you take diuretics (medicines that increase urine production) or keep low-salt diet or as a consequence of vomiting or diarrhoea.
- have aortic stenosis (narrowing of the main blood vessel leading from the heart), mitral valv stenosis (narrowing of heart’s mitral valve), hypertrophic cardiomyopathy (cardiac muscle disease) or renal artery stenosis (narrowing of the artery supplying the kidney with blood).
- have hypersensitivity reactions or tissue swelling (angioedema) during treatment with Perilex 8 mg or other ACE inhibitors.
- Angioneurotic oedema more frequently occur in patients with black skin colour than in patients with non-black skin colour.
- are going to have desensitisation treatment to reduce the effects of an allergy to bee or wasp stings
- are undergoing LDL-apheresis (which is removal of cholesterol from your blood by a machine)
- have a heart problem.
- have a liver problem.
- have a kidney problem, or have recently had a kidney transplantation
- are receiving dialysis.
- suffer from a collagen disease such as systemic lupus erythematosus or sclerodema.
- are on a salt restricted diet or use salt substitutes which contain potassium.
- suffer from a diabetes which is not well controlled
- you must tell your doctor if you think you are (or might become) pregnant. Perilex 8 mg is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).
- are breast-feeding.

Perilex 8 mg tablets are not recommended for children.

You should also inform your doctor or medical staff that you are taking Perilex 8 mg
- if you had an episode of chest pains (angina pectoris).
- if you are to undergo anaesthesia and/or surgery.
- if you have suffered from recent diarrhoea or vomiting.
- If your blood pressure is not sufficiently lowered due to your ethnic affiliation (particularly in patients with black skin colour).
- If you have a persistent dry cough.
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, herbal or natural products. In particular, you should check with your doctor if you are taking any of the following to be sure that it is safe to take Perilex 8 mg:

- Other medicines for treating high blood pressure including diuretics (water tablets)
- Potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride): potassium supplements and potassium-containing salt substitutes
- medicines for the treatment of diabetes (insulin or tablets) to lower blood sugar
- lithium for treatment of mania or depression
- medicines for the treatment of mental disorders such as depression, anxiety, schizophrenia or other psychoses.
- allopurinol used for the treatment of gout
- immunosuppressants used for the treatment of autoimmune disorders (e.g. rheumatoid arthritis) or following transplant surgery
- procainamide, a treatment for irregular heartbeat
- non-steroidal anti-inflammatory drugs (NSAIDs) medications for pain relief, including aspirin (if dose is higher or equal to 3g/day)
- medicines used for the treatment of low blood pressure, shock or asthma (e.g. ephedrine, noradrenaline or adrenaline)
- vasodilators including nitrates (a product that make the blood vessels become wider)
- heparin (blood thinning medication)

Ask your doctor if you are not sure what these medicines are.

Tell your doctor or dentist before having an anaesthetic or surgery because your blood pressure may fall suddenly during the anaesthesia.

Taking Perilex 8 mg with food and drink
It is recommended that Perilex 8 mg to be taken before a meal with sufficient amount of fluid (e.g. water) in order to reduce the influence of food on the way which the medicine works.
Potassium containing food additives or salt substitutes should not be used if you use Perilex 8 mg. The blood potassium concentration can be elevated too high. Also large amounts of (plain) salt (NaCl) in the diet may reduce the antihypertensive effect of Perilex 8 mg.

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 before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of Perindopril. Perindopril is not recommended in early pregnancy, and must not be taken when 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 is not recommended for 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.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
No studies on the effects on the ability to drive and use machines have been performed. However, Perilex 8 mg does not affect alertness but different reactions such as dizziness or weakness, in relation to the decrease in blood pressure may occur in certain patients, especially in the beginning of treatment or when increasing the dose. If affected, your ability to drive or to operate machinery may be impaired.

Important information about some of the ingredients of Perilex 8 mg
Perilex 8 mg contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE PERILEX 8 mg

Always take this medicine exactly as your doctor told you. Please ask your doctor or pharmacist if you are not sure.

Perilex 8 mg may be used on its own or with other medicines which lower blood pressure. Not all mentioned posologies are possible with the product in this Leaflet.

The usual dosages for Perilex 8 mg are as follows:
**High blood pressure:** the usual starting dose is 4 mg once daily in the morning.
In elderly patients, patients with low blood pressure or heart failure, a starting dose of 2 mg can be used.
After a month, this can be increased to 4 mg a day and if necessary to 8 mg a day.

**Stable coronary artery disease:** the usual starting dose is 4 mg once daily. After two weeks and if 4 mg is well tolerated, this can be increased to 8 mg once daily.
If you are 65 or over, the usual starting dose is 2mg once daily. After one week this can be increased to 4 mg once daily and after a further week to 8 mg once daily.
Your doctor may give you a blood test to check that your
kidneys are working properly before increasing the dose to 8 mg.
In case of impaired renal or hepatic function, your doctor will adjust the dose of Perilex 8 mg for you.
Take your tablet(s) with a glass of water, preferably at the same time each day, in the morning, before a meal. If you are taking water tablets (diuretics), your doctor may decide to reduce or even discontinue these at the beginning of your treatment with Perilex 8 mg.

Perilex 8 mg is not suitable for use in children

**If you take more Perilex 8 mg than you should**
If you take too many tablets, contact your nearest hospital casualty department or tell your doctor immediately. The most likely effect in case of an overdose is low blood pressure. If marked low blood pressure occurs (symptoms such as dizziness or faintness), lying down with the legs raised can help.

**If you forget to take Perilex 8 mg**
It is important to take your medicine every day. However, if you forget to take one or more doses, take another as soon as you remember and then go on as prescribed. Do not take a double dose.

**If you stop taking Perilex 8 mg**
Always consult your doctor, if you wish to stop taking this medicine. Even if you feel well, it may be necessary to continue taking this medicine.

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

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

This side effect occurs uncommonly (affecting less than 1 in every 100 people). However, if you notice any of the following side effects, contact your doctor immediately:

- Swelling of the face, lips, mouth, tongue or throat
- Difficulty in breathing
- Dizziness or fainting
- Unusually fast or irregular heart beat

These are symptoms of a serious reaction (angioedema) which can occur with all other drugs of this type (ACE inhibitors). It must be treated immediately, usually in hospital.
Other possible side effects

Common (affecting less than 1 in every 10 people):
- cough, shortness of breath
- light-headedness due to low blood pressure (particularly after the first few doses, if the dose is increased or when water tablets are also taken)
- headache, dizziness, vertigo, tiredness, pins and needles, muscle, cramps, visual disturbances (e.g. blurred vision, eye pain), tinnitus (sensation of noises in the ears)
- nausea, vomiting, abdominal pain, changes in your sense of taste, feeling of indigestion, diarrhoea, constipation
- skin rashes, itching
- feeling week

Uncommon (affecting less than 1 in every 100 people):
- changes in mood or sleep
- bronchospasm (tightening of the chest, wheezing and shortness of breath)
- dry mouth
- kidney problems
- impotence
- sweating

Very rare (affecting less than 1 in every 10,000 people):
- confusion
- irregular heart beat, heart attack and stroke (these have been reported with ACE inhibitors in association with low blood pressure)
- angina pectoris (chest tightness)
- eosinophilic pneumonia (a rare type of pneumonia), rhinitis (blocked up or runny nose)
- pancreatitis (inflammation of the pancreas)
- erythema multiforme (skin reaction disorder resulting from allergic reaction provoked by many different causes)
- acute kidney problems
- changes in the blood cell count: your doctor may decide to carry out blood tests at intervals to monitor for this.

Not known (cannot be estimated from the available data):
- hypoglycaemia (lowering of blood sugar)
- inflammation of blood vessels, often with skin rash

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

5. HOW TO STORE PERILEX 8 mg

Keep out of the reach and sight of children

Do not use Perilex 8 mg after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

Do not store above 25°C.
Store in the original package in order to protect from light.

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 Perilex 8 mg contains:
The active substance is: perindopril tert-butyamine.

Each tablet contains, 8 mg perindopril tert-butyamine, equivalent to 7.092mg perindopril as sodium salt (formed in situ) and equivalent to 6.676 mg of perindopril.

The other ingredients are: Microcrystalline cellulose, magnesium stearate, lactose anhydrous, maize starch and talc

What Perilex 8 mg looks like and contents of the pack

White to creamy, round, biconvex tablets.

Aluminium/Aluminium blister.

Pack sizes:
30 tablets
60 tablets
90 tablets
Not all pack sizes may be marketed.

Marketing authorization holder and Manufacturer

MAH
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia

Manufacturer
Weimer Pharma GmbH
Im Steingerüst 30, 76437 Rastatt
Germany
&
Galex d.d.
Tišinska ulica 29g
9000 Murska Sobota
Slovenia
&
PNG GEROLYMATOS S.A. (PLANT B)
4, Asklipiou str., 14568 Kryoneri Attiki
Greece

This leaflet was last approved in 07/2010.
PAR Pritnox and Perilex 2, 4 and 8mg Tablets and Peryl 4 and 8mg Tablets

Module 4
Labelling
Pritnox 2 mg tablets
perindopril tert-butylamine tablets

MAJ/AU:
Gale, d.d., Šiška ulica 25g, 9000 Maribor, Slovenia
M. A. Number: PL 53813/0001

CAUTION:
Read the enclosed literature sheet.
Keep out of the reach of children.
Do not store above 25°C. Store in the original container in order to protect from light.

Each tablet contains 2 mg perindopril tert-butylamine, expanded to 1.75 mg perindopril as tert-butylamine salt.
Each tablet also contains 1.25 mg amlodipine as amlodipine besylate.

Consult the enclosed literature sheet for further information.
PAR Pritnox and Perilex 2, 4 and 8mg Tablets and Peryl 4 and 8mg Tablets

UK/H/1625/001-3/DC, UK/H/3097/001-3/DC and UK/H/3119/001-2/DC

Pritnox 8 mg tablets

perindopril tert-butylamine
tablets

M.A. Number: PL 33815/003

Each tablet contains 8 mg perindopril tert-butylamine, equivalent to 7.000 mg perindopril as mitraull (formulated as lyophilized) and equivalent to 6.255 mg of perindopril.

Contains galactose.

See leaflet for further information.
Par Pritnox and Perilex 2, 4 and 8mg Tablets and Peryl 4 and 8mg Tablets

UK/H/1625/001-3/DC, UK/H/3097/001-3/DC and UK/H/3119/001-2/DC
Perilex 8 mg tablets
perindopril tert-butylamine

M.A.A.: GABA, d.d., Tlalska ulica 29g, 9200 Ljubljana, Slovenia
W. A. Number: PL 3381/00010

POM

Each tablet contains 8 mg perindopril tert-butylamine, equivalent to 7.02 mg perindopril as such with
5.1 mg in active and equivalent to
6.47 mg of perindopril.
Contains lactose in addition.
See leaflet for further details.
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Pritnox and Peryl 2 and 4mg Tablets and Perilex 4mg Tablets in the treatment of hypertension, heart failure and stable coronary artery disease and Pritnox, Peryl and Perilex 8mg Tablets, in the treatment of hypertension and stable coronary artery disease, could be approved.

These applications were submitted via the Decentralised Procedure (UK/H/1625/001-3/DC, UK/H/3097/001-3/DC and UK/H/3119/001-2/DC), with the UK as RMS and the following CMSs:

UK/H/1625/001/DC: Denmark, France, Luxemburg and The Netherlands
UK/H/1625/002-3/DC: Belgium, Czech Republic, Denmark, Finland, France, Hungary, Italy, Luxemburg, The Netherlands, Poland, Portugal and Slovak Republic
UK/H/3097/001-3/DC: Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovak Republic
UK/H/3119/001-2/DC: Czech Republic, Estonia, Greece, Hungary, Lithuania, Latvia, Poland, Slovenia and Slovak Republic

These applications were submitted under Article 10.1, claiming to be generic medicinal products of Coversyl 2mg, 4mg and 8mg tablets, which were first licensed to Les Laboratoires Servier, France, on 22nd June 1988. The 8mg strength was authorised in December 2003 (PL 05815/0001-2 and 23).

Perindopril is an ACE inhibitor that inhibits the conversion of angiotensin I into angiotensin II. Inhibition of ACE leads to reduced plasma level of angiotensin II which consequentially increases plasma rennin activity (by inhibition of the negative feedback of rennin release). Perindopril acts through its active metabolite, perindoprilat. Other metabolites are inactive.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of the originator products that have been licensed for over 10 years. No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of the originator products that have been licensed for over 10 years. Bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

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

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.
All member states agreed to grant respective licences for the above products at the end of procedure (Day 210 – 19th July 2010). After a subsequent national phase, the UK granted licences for these products on 18th August 2010 (PL 33815/0001-3, 0006-10).
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Pritnox and Peryl 2, 4 and 8mg Tablets and Perilex 4 and 8mg Tablets |
| Name(s) of the active substance(s) (INN) | Perindopril tery-butyramine |
| Pharmacotherapeutic classification (ATC code) | ACE inhibitors (C09A A04) |
| Pharmaceutical form and strength(s) | 2, 4 and 8mg Tablets |
| Reference numbers for the Decentralised Procedures | UK/H/1625/001-3/DC, UK/H/3097/001-3/DC, UK/H/3119/001-2/DC |
| Reference Member State | United Kingdom |
| Concerned Member States | UK/H/1625/001/DC: DK, FR, LU, NL, PL, PT, SK |
| | UK/H/1625/002-3/DC: BE, CZ, DK, FI, FR, HU, IT, LU, NL, PL, RO, SK |
| | UK/H/3097/001-3/DC: BG, CZ, HU, PL, RO, SK |
| | UK/H/3119/001-2/DC: CZ, EE, EL, HU, LT, LV, PL, SI, SK |
| Marketing Authorisation Number(s) | PL 33815/0001-3, 0006-0010 |
| Name and address of the authorisation holder | Galex d.d. |
| | Tišinska ulica 29g |
| | 9000 Murska Sobota |
| | Slovenia |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

DRUG SUBSTANCE

INN: Perindopril tert-butylamine
Chemical Name: 2-Methylpropan-2-amine (2S,3aS,7aS)-1-[(2S)-2-[[1S]-1-

Structure:

Molecular Formula: C_{23}H_{43}N_{3}O_{5}
Molecular Weight: 441.6
Appearance: A white or almost white, slightly hygroscopic, crystalline powder.
Solubility: Freely soluble in water and in ethanol (96%), soluble or sparingly soluble in methylene chloride.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.
DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients lactose anhydrous, maize starch, microcrystalline cellulose, talc and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose anhydrous, none of the excipients are sourced from animal or human origin. TSE/BSE declarations are provided from the supplier of this excipient. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Coversly 2, 4 and 8mg Tablets, which were first granted to Les Laboratoires Servier, France, on 22nd June 1988 (2mg and 4mg Tablets) and December 2003 (8mg Tablets).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packed in Aluminium/Aluminium blister. Pack sizes are 10, 30, 60 and 90 Tablets (Pritnox) and 30, 60 and 90 Tablets (Peryl and Perilex)

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set for these products, with special storage conditions ‘Do not store above 25°C’ and ‘Store in the original container in order to protect from light’.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL 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. 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 aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
These applications claim to be generic medicinal products of Coversyl 2mg, 4mg and 8mg tablets, which have been licensed within the EU for over 10 years.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of a detailed environmental risk assessment. This is satisfactory.

There are no objections to the approval of these products from a preclinical point of view.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

This was a single centre, open-label, randomised, single-dose, two-way crossover study comparing the pharmacokinetics of the test product Perindopril sodium 8mg tablet (Galex d.d., Slovenia) versus the reference product Coversyl 8mg Tablet (Les Laboratoires Servier, France) in healthy subjects under fasting conditions.

The washout period was 28 days and the sampling period was up to 72 hours post-dose.
Results
The summary results from this study for perindopril and metabolite perindoprilat are shown in the tables below.

### Perindopril Sodium (A) vs Coversyl (B)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ratio</th>
<th>90% Geometric C.I.</th>
<th>Intra-Subject CV</th>
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<tbody>
<tr>
<td><strong>AUC&lt;sub&gt;0-t&lt;/sub&gt;</strong></td>
<td>104.88%</td>
<td>100.02% to 109.98%</td>
<td>11.59%</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;0-inf&lt;/sub&gt;</strong></td>
<td>104.99%</td>
<td>100.20% to 110.01%</td>
<td>11.41%</td>
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<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>106.77%</td>
<td>99.14% to 114.99%</td>
<td>18.19%</td>
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</table>

\[1\text{Calculated using least-squares means according to the formula: } \times 100.\]

\[2\text{90% Geometric Confidence Interval using ln-transformed data.}\]

### Perindoprilat - Perindopril Sodium (A) vs Coversyl (B)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ratio</th>
<th>90% Geometric C.I.</th>
<th>Intra-Subject CV</th>
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<tbody>
<tr>
<td><strong>AUC&lt;sub&gt;0-72h&lt;/sub&gt;</strong></td>
<td>103.56%</td>
<td>100.38% to 106.84</td>
<td>7.61%</td>
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<tr>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>103.71%</td>
<td>96.75% to 111.17%</td>
<td>17.03%</td>
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\[1\text{Calculated using least-squares means according to the formula: } \times 100.\]

\[2\text{90% Geometric Confidence Interval using ln-transformed data.}\]

The 90% confidence intervals for C<sub>max</sub> and AUC were within the pre-defined limits. Bioequivalence has been shown for the test formulation (Perindopril 8mg tablets) and the reference formulation (Coversyl 8mg Tablets). The extrapolation of results from the BE study conducted with the 8mg strength tablet to the lower strength formulations has been appropriately justified and is acceptable.

Pharmacodynamics
No new data have been submitted and none are required.

Clinical Efficacy
No new data have been submitted and none are required.

Clinical Safety
No new data have been submitted and none are required.

Expert Report
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

Module 1 – Administrative information
Marketing Authorisation Application forms (MAA)
The MAA forms are medically satisfactory.

Summary of Product Characteristics (SmPC)
The SmPCs are medically satisfactory and consistent with that for the reference product.

Patient Information Leaflet (PIL)
The PIL is medically satisfactory and consistent with the SPC.

Packaging
The packaging is medically satisfactory.

Conclusion
There are no objections to the approval of these products from a clinical point of view.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Pritnox and Perilex 2, 4, and 8mg Tablets and Peryl 4 and 8mg 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 these type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Perindopril 8mg tablets and the reference product Coversyl 8mg Tablets. The results could be extrapolated to the lower strengths 2mg and 4mg Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Perindopril tert-butylamine is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
### Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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