APPROVED SPC

For

PREXUM 5+10 mg

Registration No.:

Prexum® 5 mg: A39/7.1.3/0232

Prexum® 10 mg: A39/7.1.3/0233

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Confidential Information

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Prexum 5 mg and 10 mg

PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

Prexum 5 mg, film-coated tablet.

Prexum 10 mg, film-coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **Prexum 5 mg**, film-coated tablet contains 5 mg perindopril arginine salt.

Excipients with known effect: 72,58 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

Each **Prexum 10 mg**, film-coated tablet contains 10 mg perindopril arginine salt.

Excipients with known effect: 145,16 mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prexum 5 mg Film-coated tablet.

Light-green, rod-shaped film-coated tablet engraved with on one face and scored on both edges. The tablet can be divided into equal doses.

Prexum 10 mg Film-coated tablet.

Green, round, biconvex, film-coated tablet engraved with on one face and on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prexum 5 mg and 10 mg are indicated for the treatment of mild to moderate hypertension.

Prexum 5 mg is indicated in congestive heart failure not adequately controlled by conventional therapy with diuretics and digitalis and in whom vasodilatation is indicated.

4.2 Posology and method of administration

Posology

Mild to moderate hypertension

The recommended dosage is 5 mg orally taken in the morning before breakfast, which can be increased to a single daily dose of 10 mg if necessary, after one month of treatment.
In elderly patients, treatment should be initiated at a dose of 2,5 mg, which may progressively be increased to 5 mg after one month, then to 10 mg if necessary, depending on renal function.

Congestive heart failure

The treatment should be initiated under close medical supervision. Initial dose of 2,5 mg orally as a single daily dose in the morning, which may, in most instances be increased to 5 mg (once blood pressure acceptability has been demonstrated).

Concomitant diuretic therapy in hypertension

Caution is recommended in patients who are currently being treated with diuretics. As the effects of ACE-inhibitors may be potentiated in a situation where hypovolaemia may occur, the diuretic therapy should be discontinued 2 to 3 days prior to initiation of therapy with **Prexum.** In the case of combination with a diuretic, it is not advisable to prescribe a potassium salt or a potassium sparing agent before determining the blood potassium, and attention should be paid to possible overdose of the diuretic.

Special populations

Renal insufficiency

In patients with renal insufficiency, the dosage of perindopril must be adjusted in relation to the severity of the insufficiency.

Table 1 Dosage adjustment in renal impairment

Creatinine clearance	**Recommended dosage**
> 60 ml/min	5 mg per day
Between 30 and 60 ml/min	2,5 mg per day
Between 15 and 30 ml/min	2,5 mg every other day
Haemodyalised patients	
< 15 ml/min	2,5 mg on day of dialysis

Perindopril is dialysable (70 ml/min).

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

Patients with hepatic impairment

No dosage adjustment is necessary in patients with hepatic impairment.

Paediatric population

The safety and efficacy of perindopril in children and adolescents aged below 18 years have not been established.

Method of administration

For oral use.

Prexum is recommended to be taken once daily in the morning before a meal.

4.3 Contraindications

- Hypersensitivity to any of the ingredients of **Prexum**
- A history of angioedema related to previous therapy with ACE-inhibitors or angiotensin receptor blockers (ARBs): these patients must never again be given these medicines. (see section 4.4)
- Hereditary/idiopathic angioedema (see section 4.4)
- Hypertrophic obstructive cardiomyopathy (HOCM) (see section 4.4)
- Severe renal function impairment (creatinine clearance below 30 ml/min)
- In bilateral renal artery stenosis
- Renal artery stenosis in patient with a single kidney
- Aortic stenosis (see section 4.4)
- Concomitant therapy with potassium-sparing diuretics (such as spironolactone, triamterene, amiloride), (see section 4.5)
- Porphyria
- In combinations with lithium: concomitant use with **Prexum** may lead to toxic blood concentration of lithium (see section 4.5)
- Pregnancy and lactation (see section 4.6)
- The concomitant use of **Prexum** with aliskiren-containing products is contraindicated. (see sections 4.4 and 4.5)
- Concomitant use with sacubitril/valsartan (see sections 4.4 and 4.5). **Prexum** must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.4 and 4.5)
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
- Concomitant use of fluoroquinolones with ACE-inhibitors/Renin angiotensin receptor blockers is contraindicated in patients with moderate to severe renal failure (Creatinine Clearance ≤ 30 ml/min) and in elderly patients.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **Prexum**, the treatment must be stopped promptly and switched to a different medicine. (see sections 4.3 and 4.6).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure).

Dual blockade of RAAS through the combined use of **Prexum**, angiotensin II receptor blockers or aliskiren is therefore contraindicated (see sections 4.3 and 4.5).

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

Prexum and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy (see sections 4.3 and 4.5). NS).

Hypotension

ACE-inhibitors may cause a fall in blood pressure. Symptomatic hypotension is rarely seen 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 with an increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored (see sections 4.2 and 4.8). Similar considerations apply to patients with

ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contra-indication 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 **Prexum.** If hypotension becomes symptomatic, a reduction of the dose or discontinuation of perindopril may be necessary.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy

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

Renal impairment

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

In patients with bilateral renal artery stenosis, or stenosis of the artery to a solitary kidney, and who have been treated with ACE-inhibitors, increases in blood urea and serum creatinine may occur. This is usually reversible upon discontinuation of therapy. It 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 **Prexum** therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, especially when **Prexum** was 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 **Prexum** may be required.

Haemodialysis patients

Anaphylactic 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 **Prexum** in patients with a recent kidney transplant.

Renovascular hypertension

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

Hypersensitivity/Angioedema

Angioedema of the face, lips, mucous membranes, tongue, glottis and/or larynx, and extremities has been reported, in patients treated with ACE-inhibitors, including **Prexum** (see section 4.8). This may occur at any time during therapy. In such cases, **Prexum** should immediately be discontinued and appropriate monitoring should be initiated and continued until the symptoms have disappeared completely. 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, and is likely to cause airway obstruction, emergency therapy should immediately be administered. This may include the administration of adrenaline and/or the maintenance of the patient's airway. The patient should be under close medical supervision until the symptoms have disappeared.

ACE-inhibitors cause a higher rate of angioedema in black patients than in other ethnic groups.

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

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

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see sections 4.3 and 4.5). Sacubitril/valsartan must not be initiated until 36 hours after taking the last dose of perindopril therapy. If treatment with

sacubitril/valsartan is stopped, perindopril therapy must not be initiated until 36 hours after the last dose of sacubitril/valsartan (see section 4.3 and 4.5).

Concomitant use of ACE inhibitors with other NEP inhibitors (e.g. racecadotril), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) in a patient already taking an ACE-inhibitor.

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment, with fluoroquinolones or ACE-inhibitors/Renin angiotensin receptor blockers, whether used separately and/or concomitantly.

Anaphylactic reactions during low-density lipoproteins (LDL) apheresis

Patients receiving ACE-inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have rarely experienced life-threatening anaphylactic reactions. These reactions were avoided by temporarily withholding ACE-inhibitors therapy prior to each apheresis.

Anaphylactoid reactions during desensitisation

Patients receiving ACE-inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactic reactions. These reactions were avoided when the ACE-inhibitors were temporarily withheld, but they reappeared upon re-challenge.

Hepatic failure

ACE-inhibitors have been associated with a syndrome that starts with cholestatic jaundice and suddenly progresses to 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 **Prexum** and receive appropriate medical follow-up (see section 4.8).

Neutropenia/agranulocytosis/thrombocytopenia/anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors. In patients with normal renal function and no other complicating factors, neutropenia rarely occurs. **Prexum** 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 **Prexum** is used in such patients, periodic monitoring of the white blood cell count 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 other ethnic groups. **Prexum** may be less effective in lowering blood pressure in black people than in

other ethnic groups, possibly because of a higher prevalence of low-renin levels 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-inhibitors 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, **Prexum** 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 **Prexum**. ACE-inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole). and especially aldosterone antagonists or angiotensin-receptor blockers. The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum

potassium. Hyperkalaemia can cause serious, sometimes fatal dysrhythmias. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored. If concomitant use of the above-mentioned agents is deemed necessary, regular monitoring of serum potassium is recommended (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 ACE-inhibitors (see section 4.5).

Lithium

The combination of lithium and **Prexum** is contraindicated (see sections 4.3 and 4.5).

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

The combination of **Prexum** and potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes is generally not recommended (see section 4.5).

Primary aldosteronism

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

Excipients

Lactose intolerance

Prexum contains lactose**. Prexum** should not be administered to patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia the Lapp lactase deficiency or glucose-galactose malabsorption.

Level of sodium

Prexum contains less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Dual blockade of the RAAS with ARBs, ACE-inhibitors, or aliskiren

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

Medicines increasing the risk of angioedema

Concomitant use of ACE-inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4). Sacubitril/valsartan must not be started until 36 hours after taking the last dose of perindopril therapy. Perindopril therapy must not be started until 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.4).

Concomitant use of ACE-inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and gliptins (e.g. linagliptin, saxagliptin, sitagliptin, vildagliptin) may lead to an increased risk for angioedema (see section 4.4).

Medicines inducing hyperkalaemia

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with **Prexum.** Some medicines or therapeutic classes may

increase the occurrence of hyperkalaemia: aliskiren, potassium salts, potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), ACE-inhibitors, angiotensin-II receptors antagonists, NSAID's, heparins, immunosuppressant agents such as ciclosporin or tacrolimus and trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. The combination of these medicines increases the risk of hyperkalaemia. Therefore, the combination of **Prexum** with the above-mentioned medicines is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Concomitant use contraindicated (See section 4.3)

Aliskiren

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

Extracorporeal treatments

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitrile membranes) and low-density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers may precipitate acute kidney injury (see section 4.3).

The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Concomitant use not recommended (see section 4.4)

Aliskiren

In patients other than diabetic or impaired renal patients, risk of hyperkalaemia, worsening of renal function and cardiovascular morbidity and mortality increase (See section 4.4).

Concomitant therapy with ACE-inhibitor and angiotensin-receptor blocker

Patients with established atherosclerotic disease, heart failure, or with diabetes with end organ damage, concomitant therapy with an ACE-inhibitor and an angiotensin-receptor blocker is associated with a higher frequency of hypotension, syncope, hyperkalaemia, and worsening renal function (including acute renal failure) as compared to use of a single renin-angiotensin-aldosterone system agent. Dual blockade (e.g., by combining an ACE-inhibitor with an angiotensin II receptor antagonist) should be limited to individually defined cases with close monitoring of renal function, potassium levels, and blood pressure (see section 4.4).

Estramustine

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

Potassium sparing diuretics, (e.g. triamterene, amiloride,...), potassium (salts) containing salt substitutes

Hyperkalaemia may occur in some patients treated with **Prexum**. Potassium sparing diuretics (e.g. triamterene or amiloride), potassium supplements or potassium-containing salt substitutes, may lead to significant increases in serum potassium. The combination of **Prexum** with the above-mentioned medicines is not recommended (see section 4.4). If

concomitant use is indicated because of confirmed hypokalaemia, they should be used with caution and serum potassium should frequently be monitored.

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. Combination of **Prexum** with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.3 and 4.4).

Concomitant use which requires special care

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 the risk of hypoglycaemia. This phenomenon appeared to be more likely during the first weeks of combined treatment and in patients with renal impairment.

Baclofen

Increased antihypertensive effect. Monitor blood pressure and adapt antihypertensive dosage if necessary.

Non-potassium-sparing diuretics

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

In arterial hypertension

When prior diuretic therapy can have caused salt/volume depletion, either the diuretic must be discontinued before initiating the ACE-inhibitor, in which case a non-potassium-sparing diuretic can be thereafter reintroduced or the ACE-inhibitor must be initiated with a low dosage and progressively increased.

In diuretic-treated congestive heart failure

Prexum should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.

In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE-inhibitor therapy.

Potassium-sparing diuretics (eplerenone, spironolactone)

With eplerenone or spironolactone at doses between 12,5 mg to 50 mg by day and with low doses of ACE-inhibitors:

In the treatment of class II-IV heart failure (NYHA) with an ejection fraction < 40 %, and previously treated with ACE-inhibitors and loop diuretics, risk of hyperkalaemia, potentially lethal, especially in case of non-observance of the prescription recommendations on this combination.

Before initiating the combination, check the absence of hyperkalaemia and renal impairment.

A close monitoring of the potassium and creatinine is recommended in the first month of the treatment once a week at the beginning and, monthly thereafter.

Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid ≥ 3 g/day

The administration of non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs)

may reduce the antihypertensive effect of ACE-inhibitors. Additionally, NSAIDs and ACE-inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Acute renal failure may occur, especially in patients with compromised renal function like the elderly or dehydrated patients.

Concomitant use which requires some care

Antihypertensive agents and vasodilators

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

Tricyclic antidepressants/antipsychotics/anaesthetics

Concomitant use of certain anaesthetic medicines, 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 **Prexum**.

Gold

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Prexum is contraindicated during pregnancy and lactation.

Pregnant women should be informed of the potential hazards to the foetus and must not take **Prexum** during pregnancy (see section 4.3). 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 **Prexum** should be stopped immediately and if appropriate, alternative therapy should be started.
Foetal exposure to ACE-inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spins bifida) and of kidney malformations.
ACE-inhibitors, such as **Prexum** pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regularity mechanisms.
Oligohydramnios as well as hypotension, oliguria and anuria in newborns have been reported after administration of ACE-inhibitors in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.
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 section 4.3).

Lactation

It is not known whether perindopril is excreted into human breast milk. Therefore, the use of **Prexum** is not recommended in women who are breastfeeding. **Prexum** is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

There was no effect on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines

Prexum 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.

4.8 Undesirable effects

a. Summary of safety profile.

The safety profile of perindopril is consistent with the safety profile of ACE-inhibitors:
The most frequent adverse events reported in clinical trials and observed with perindopril are: dizziness, headache, paraesthesia, vertigo, visual disturbances, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, diarrhoea, dysgeusia, dyspepsia, nausea, vomiting, pruritis, rash, muscle cramps, and asthenia.

b. Tabulated list of adverse reactions.

The following side effects have been observed during treatment with **Prexum** and ranked under the following *frequency*

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000); including isolated reports, not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**
Blood and the lymphatic System Disorders	Eosinophilia	Uncommon*
	Agranulocytosis or pancytopenia	Very rare
	Haemoglobin decreased and haematocrit decreased	Very rare
	Leucopenia/neutropenia	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see section 4.4)	Very rare
	Thrombocytopenia	Very rare
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Rare
Metabolism and	Hypoglycaemia (see sections 4.4 and 4.5)	Uncommon*

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**
Nutrition Disorders	Hyperkalaemia, reversible on discontinuation (see section 4.4)	Uncommon*
	Hyponatraemia	Uncommon*
Psychiatric disorders	Depression	Uncommon*
	Mood disturbances	Uncommon
	Sleep disorder	Uncommon
Nervous System disorders	Dizziness	Common
	Headache	Common
	Paraesthesia	Common
	Vertigo	Common
	Somnolence	Uncommon*
	Syncope	Uncommon*
	Confusion	Very rare
Eye Disorders	Visual disturbances	Common
Ear and labyrinth disorders	Tinnitus	Common
Cardiac Disorders	Dysrhythmia	Very rare
	Palpitations	Uncommon*
	Tachycardia	Uncommon*
	Angina pectoris (see section 4.4)	Very rare
	Myocardial infarction, possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	Very rare
Vascular Disorders	Hypotension (and effects related to hypotension)	Common
	Vasculitis	Uncommon*
	Flushing	Rare*
	Stroke possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	Very rare
	Raynaud’s phenomenon	Not known
Respiratory, Thoracic and Mediastinal Disorders	Cough	Common
	Dyspnoea	Common
	Bronchospasm	Uncommon
	Eosinophilic pneumonia	Very rare
	Rhinitis	Very rare
Gastro-intestinal	Abdominal pain	Common

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**
Disorders	Constipation	Common
	Diarrhoea	Common
	Dysgeusia	Common
	Dyspepsia	Common
	Nausea	Common
	Vomiting	Common
	Dry mouth	Uncommon
	Pancreatitis	Very rare
Hepato-biliary Disorders	Hepatitis either cytolytic or cholestatic (see section 4.4)	Very rare
Skin and Subcutaneous Tissue Disorders	Pruritis	Common
	Rash	Common
	Urticaria (see section 4.4)	Uncommon
	Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see section 4.4)	Uncommon
	Photosensitivity reactions	Uncommon*
	Pemphigoid	Uncommon*
	Hyperhidrosis	Uncommon
	Psoriasis aggravation	Rare*
	Erythema multiforme	Very rare
Musculoskeletal And Connective Tissue Disorders	Muscle cramps	Common
	Arthralgia	Uncommon*
	Myalgia	Uncommon*
Renal and Urinary Disorders	Renal insufficiency	Uncommon
	Acute renal failure	Rare
	Anuria/Oliguria	Rare*
Reproductive System and Breast Disorders	Erectile dysfunction	Uncommon
General Disorders and Administration Site Condition	Asthenia	Common
	Chest pain	Uncommon*
	Malaise	Uncommon*
	Oedema peripheral	Uncommon*
	Pyrexia	Uncommon*
Investigations	Blood urea increased	Uncommon*
	Blood creatinine increased	Uncommon*
	Blood bilirubin increased	Rare

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**
	Hepatic enzyme increased	Rare
Injury, poisoning and procedural complications	Fall	Uncommon*

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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 an overdose is an intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. **Prexum** may be removed from the general circulation by haemodialysis. Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously. Expected symptoms and signs would be linked to hypotension. Further treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, plain, ATC code: C09A A04

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro. 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).
The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours.
In terms of trough versus peak blood pressure effect, the trough effect ranges between 75 – 100 % of peak effects.
Maximum effect is achieved within a month and persists without the occurrence of tachyphylaxis.
Reduction in blood pressure in patients treated with perindopril was accompanied by a reduction in peripheral resistance with no significant changes in heart rate or glomerular filtration rate. An increase in the compliance of large arteries was also observed, suggesting a direct effect on arterial smooth muscle. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged.

5.2 Pharmacokinetic properties

Following oral administration, the absorption of perindopril is rapid and the peak concentration complete within 1 hour. The plasma half-life of perindopril is equal to 1 hour. The bioavailability of perindoprilat, the active metabolite, is 27 %. Apart from active perindoprilat, perindopril gives rise to 5 metabolites, all of which are inactive.

The peak concentration of perindoprilat, the active metabolite, is reached within 3 to 4 hours and peak pharmacological activity is obtained within 4 to 6 hours.

The ingestion of food decreases conversion to perindoprilat, and hence bioavailability. Therefore, perindopril should be administered orally as a single daily dose in the morning before breakfast. The volume of distribution is approximately 0,2 l/kg for unbound perindoprilat. Protein binding is slight (binding of perindoprilat to plasma proteins is 20 %, principally to angiotensin converting enzyme), but is concentration dependent.

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

Elimination of perindoprilat is slower in the elderly, as well as in patients with heart or renal failure. In such patients, dosage adjustment should be made in relation to the degree of reduction in creatinine clearance.

Dialysis clearance of perindoprilat is equal to 70 ml/min.

Perindopril kinetics is 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Lactose monohydrate

Magnesium stearate

Maltodextrin

Hydrophobic colloidal silica

Sodium starch glycolate (type A)

Film-coating

Glycerol

Hypromellose

Copper chlorophyllin

Macrogol 6 000

Magnesium stearate

Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 ˚C in a dry place.

Keep out of reach of children.

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

6.5 Nature and contents of container

Prexum is packed into pack sizes of 30 tablets into a polypropylene white tube with a low-density polyethylene flow reducer and a low-density polyethylene white stopper, containing 2 g of white desiccant gel and placed into an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Servier Laboratories South Africa (Pty) Ltd

3rd Floor, Building J

Hertford Office Park

90 Bekker Road

Vorna Valley

Midrand

2196

8. REGISTRATION NUMBER

Prexum 5 mg: A39/7.1.3/0232

Prexum 10 mg: A39/7.1.3/0233

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 November 2005

10. DATE OF REVISION OF THE TEXT

29 April 2022

Namibia Details	
Prexum 5:	07/7.1.3/0102 (NS2)
Prexum 10:	07/7.1.3/0103 (NS2)

Botswana Details	
Prexum 5:	BOT2500122 (S2)
Prexum 10:	BOT2500140 (S2)