APPROVED SPC

For

PREXUM 10 PLUS

Registration No.: 43/7.1.3/0971

Date Approved: November 2022

Confidential Information

Prexum 10 Plus

SCHEDULING STATUS **S3**

1. NAME OF THE MEDICINE

Prexum 10 Plus film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg perindopril arginine salt and 2,5 mg indapamide.
Excipient with known effect 142,66 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prexum 10 Plus: White, round film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prexum 10 Plus is indicated for the treatment of hypertension in patients already controlled on the individual components at the same dosages, and in patients not adequately controlled on monotherapy of the individual components.

4.2 Posology and method of administration

Posology

One **Prexum 10 Plus** film-coated tablet per day as a single dose, preferably to be taken in the morning, and before a meal.

Special populations

Elderly

In elderly, the plasma creatinine must be adjusted in relation to age, weight and gender. Elderly patients can be treated if renal function is normal and after considering blood pressure response.

Patients with renal impairment

In moderate to severe renal impairment (creatinine clearance below 60 ml/min), treatment is contraindicated. Usual medical follow-up will include frequent monitoring of creatinine and potassium.

Patients with hepatic impairment

In severe hepatic impairment, treatment is contraindicated.

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

Children and adolescents

Prexum 10 Plus should not be used in children and adolescents as the efficacy and tolerability of perindopril in children and adolescents, alone or in combination, have not been established.

4.3 Contraindications

Perindopril

- Hypersensitivity to any of the ingredients of **Prexum 10 Plus**
- 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 or idiopathic angioedema. (see section 4.4)
- Hypertrophic obstructive cardiomyopathy (HOCM) (see section 4.4)
- Severe renal function impairment (creatinine clearance below 30 ml/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis (see section 4.4)
- Concomitant therapy with potassium-sparing medicines such as spironolactone, triamterene, amiloride (see section 4.5)
- Porphyria
- Lithium therapy: concomitant administration with **Prexum 10 Plus** may lead to toxic blood concentrations of lithium (see section 4.5)
- Concomitant use of **Prexum 10 Plus** with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73 m²) (see sections 4.4 and 4.5)
- Concomitant use with sacubitril/valsartan therapy. **Prexum 10 Plus** 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)
- Significant bilateral renal artery stenosis or stenosis of the artery to a single functioning Pregnancy and lactation (see section 4.6

- 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.

Indapamide

- Hypersensitivity to indapamide or to any other sulphonamides
- Severe and moderate renal impairment (creatinine clearance below 60 ml/min)
- Hepatic encephalopathy
- Severe hepatic impairment
- Hypokalaemia
- Concomitant use with non-antidysrhythmic medicines causing *torsades de pointes* (see section 4.5)
- Lactation. (see section 4.6).

Prexum 10 Plus

- Hypersensitivity to any of the components of **Prexum 10 Plus**

Due to the lack of sufficient therapeutic experience, **Prexum 10 Plus** should not be used in:

- Dialysis patients
- Patients with untreated decompensated heart failure.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **Prexum 10 Plus**, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine.

Special warnings

Common to perindopril and indapamide

Lithium

The combination of lithium and the combination of perindopril and indapamide is contraindicated (see section 4.3 and 4.5).

Perindopril

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

There is evidence that the concomitant use of ACE-inhibitors such as **Prexum 10 Plus**, angiotensin II receptor blockers (ARBs) or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of

RAAS through the combined **Prexum 10 Plus**, angiotensin II receptor blockers or and aliskiren is therefore contraindicated (see section 4.3). If dual blockade therapy is considered necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
Prexum 10 Plus and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy (see sections 4.5 and 4.8).

Potassium-sparing medicines, potassium supplements or potassium-containing salts substitutes
The combination of **Prexum 10 Plus** and potassium-sparing medicines, potassium supplements or potassium-containing salt substitutes is not recommended (see sections 4.3 and 4.5).

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 10 Plus** should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these risk factors, especially if there is pre-existing impaired renal function. These patients developed serious infections, which may not respond to intensive antibiotic therapy. If **Prexum 10 Plus** 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 and fever) (see sections 4.5 and 4.8).

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 perindopril (see section 4.8). This may occur at any time during therapy. In such cases, **Prexum 10 Plus** should immediately be discontinued, and appropriate therapy and monitoring should be initiated and continued until the symptoms have completely disappeared.

Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine (adrenaline) solution 1:1 000 (0,3 ml to 0,5 ml) and/or measures to ensure a patent airway, should be administered promptly.
Black patients receiving ACE-inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.
Patients with a history of angioedema unrelated to ACE-inhibitor therapy may be at increased risk of angioedema while receiving an ACE-inhibitor such as contained in **Prexum 10 Plus** (see section 4.3).
Intestinal angioedema has been reported 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 **Prexum 10 Plus** presenting with abdominal pain.

The combination of perindopril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see section 4.3).
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 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.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis
Patients receiving ACE-inhibitors such as contained in **Prexum 10 Plus** 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 such as contained in **Prexum 10 Plus** during desensitisation treatment hymenoptera (bees, wasps) venom have experienced anaphylactic reactions. **Prexum 10 Plus** should be used with caution in allergic patients treated with desensitisation and avoided in those undergoing venom immunotherapy. These reactions were avoided when the ACE-inhibitors were temporarily withheld for at least 24 hours before treatment in patients who require both ACE-inhibitors and desensitisation.

Haemodialysis patients

Anaphylactic reactions have been reported in patients dialysed with high flux membranes, (e.g., AN 69®) 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 medicine.

Primary aldosteronism

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

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.

Indapamide

Hepatic encephalopathy

When liver function is impaired, thiazide diuretics and thiazide-related diuretics may cause, particularly in case of electrolyte imbalance, hepatic encephalopathy which can progress to hepatic coma. Administration of the diuretic should be stopped immediately if this occurs.

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazides and related thiazides diuretics such as indapamide (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is

deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Precautions for use

Common to perindopril and indapamide

Renal impairment

In cases of moderate to severe renal impairment (creatinine clearance < 60 ml/min), treatment is contraindicated.

In certain hypertensive patients without pre-existing apparent renal lesions and for whom renal blood tests show functional renal insufficiency, treatment should be stopped and possibly restarted either at a low dose or with one constituent only.

In these patients, usual medical follow-up will include frequent monitoring of potassium and creatinine, after two weeks of treatment and then every two months during therapeutic stability period. Renal failure has been reported mainly in patients with severe heart failure or underlying renal failure including renal artery stenosis.

Prexum 10 Plus should not be used in case of bilateral renal artery stenosis or a single functioning kidney (see section 4.3).

Hypotension and water and electrolyte depletion

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

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

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

Potassium levels

The combination of perindopril and indapamide such as in **Prexum 10 Plus** does not prevent the onset of hypokalaemia, particularly in diabetic patients or in patients with renal failure. Regular monitoring of plasma potassium levels should be carried out.

Level of sodium

Prexum 10 Plus contains less than 1 mmol sodium (23 mg) per tablet, i.e., essentially ‘sodium-free’.

Perindopril

Cough

A dry cough has been reported with the use of angiotensin converting enzyme inhibitors such as contained in **Prexum 10 Plus**. It is characterised by its persistence and by its disappearance when treatment is withdrawn. An iatrogenic aetiology should be considered in the event of this symptom. If **Prexum 10 Plus** is still preferred, and if the patient can tolerate the cough, continuation of treatment may be considered.

Paediatric population

The efficacy and tolerability of perindopril inhibitors such as contained in **Prexum 10 Plus** in children and adolescents, alone or in combination, have not been established.

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

Marked stimulation of the renin-angiotensin-aldosterone system has been observed particularly during marked water and electrolyte depletions (strict sodium e restricted diet or prolonged diuretic treatment), in patients whose blood pressure was initially low, in cases of renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites.
Blocking of this system by **Prexum 10 Plus** may therefore cause, particularly at the time of the first administration and during the first two weeks of treatment, a sudden drop in blood pressure and/or an increase in plasma levels of creatinine, showing a functional renal insufficiency. Occasionally this can be acute in onset, and with a variable time to onset.
In such cases, the treatment should then be initiated at a lower dose and increased progressively.

Elderly

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

Atherosclerosis

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

Renovascular hypertension

The treatment for renovascular hypertension is revascularisation. Nonetheless, angiotensin converting enzyme inhibitors can be beneficial in patients presenting with renovascular hypertension who are awaiting corrective surgery or when such a surgery is not possible.
Treatment with **Prexum 10 Plus** is contraindicated in patients with renal artery stenosis.
Treatment with **Prexum 10 Plus** is not appropriate in patients with known or suspected renal artery stenosis because treatment should be started in a hospital setting at a dose lower than the **Prexum 10 Plus** one.

Cardiac failure/severe cardiac insufficiency

In patients with severe cardiac insufficiency (grade IV), treatment with **Prexum 10 Plus** is not appropriate because treatment should be started under medical supervision with a reduced initial dose. Treatment with beta-blockers in hypertensive patients with coronary insufficiency should not be stopped; **Prexum 10 Plus** should be added to the beta-blocker.

Diabetic patients

In patients with insulin dependent diabetes mellitus (spontaneous tendency to increased levels of potassium), treatment with **Prexum 10 Plus** is not appropriate because treatment should be started under medical supervision with a reduced initial dose.
The glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic medicines or insulin, especially during the first month of treatment with an ACE-inhibitor such as contained in **Prexum 10 Plus** (see section 4.5).

Ethnic differences

ACE-inhibitors, including, perindopril is apparently 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.

Surgery/anaesthesia

ACE-inhibitors can cause hypotension in cases of anaesthesia, especially when the anaesthetic administered is a medicine with hypotension potential.
It is therefore recommended that treatment with long-acting ACE-inhibitors such as perindopril should be discontinued where possible one day before surgery.

Aortic stenosis / hypertrophic cardiomyopathy

Prexum 10 Plus should not be used in patients with an obstruction in the outflow tract of the left ventricle. **Prexum 10 Plus** is contraindicated in aortic stenosis (see section 4.3).

Hepatic failure

ACE-inhibitors have been associated with a syndrome that starts with cholestatic jaundice and suddenly progresses to hepatic necrosis which may be fatal. The mechanism of this syndrome is not understood. Patients receiving **Prexum 10 Plus** who develop jaundice or marked elevations of hepatic enzymes should discontinue the **Prexum 10 Plus** and receive appropriate medical follow-up.

Hyperkalaemia

Elevations in serum potassium have been observed in some patients treated with ACE-inhibitors, including perindopril**.** ACE-inhibitors can cause hyperkalaemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. Patients at risk 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, amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparins, co-trimoxazole also known as trimethoprim/sulfamethoxazole, other ACE-inhibitors, angiotensin-II receptor antagonists, acetylsalicylic acid ≥ 3 g/day, COX-2 inhibitors and non-selective NSAID's, immunosuppressant medicines such as ciclosporin or tacrolimus, trimethoprim) 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 medicines is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see section 4.5).

Indapamide

Water and electrolyte balance

Sodium levels

These should be tested before treatment is started, then at regular intervals. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients (see sections 4.8 and 4.9).
Any diuretic treatment may cause hyponatraemia, sometimes with very serious consequences. Hyponatraemia with hypovolaemia may be responsible of dehydration and orthostatic hypotension. Concomitant loss of chloride ions may lead to secondary compensatory metabolic alkalosis the incidence and degree of this effect are slight.

Potassium levels

Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics such as indapamide. Hypokalaemia may cause muscle disorders. Cases of Rhabdomyolysis have been reported, mainly in the context of severe hypokalaemia. The risk of onset of lowered potassium levels (< 3,4 mmol/l) should be prevented in high-risk populations such as elderly and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure.
In such cases hypokalaemia increases the cardiac toxicity of cardiac glycosides and the risk of cardiac rhythm disorders.
Subjects presenting with a long QT interval are also at risk, whether the origin is congenital or iatrogenic. Hypokalaemia, as with bradycardia, acts as a factor which favours the onset of severe cardiac rhythm disorders, in particular *torsades de pointes*, which may be fatal.
In all cases more frequent testing of potassium levels is necessary. The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment. If low potassium levels are detected, correction is required. Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected

Calcium levels

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

Plasma magnesium

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8).

Blood glucose

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

Uric acid

Tendency to gout attacks may be increased in hyperuricaemic patients.

Renal function and diuretics

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

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

cl_{cr} = (140 - age) x body weight / 0,814 x plasma creatinine level with

age expressed in years

body weight in kg

plasma creatinine level in micromol/l

This formula is suitable for an elderly male and should be adapted for women by multiplying the result by 0,85.

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

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulphonamide or sulphonamide derivative medicines can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue the medicine intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Athletes

Athletes should be aware that this product contains indapamide, which may give a positive reaction in drug tests.

Lactose intolerance

Prexum 10 Plus contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **Prexum 10 Plus**.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use with Prexum 10 Plus is not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE-inhibitors. The combination use of **Prexum 10 Plus** with lithium is contraindicated (see section 4.3).

Concomitant use with Prexum 10 Plus which requires special care

Baclofen

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

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

When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory medicines (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.

Concomitant use with Prexum 10 Plus which requires some care

Imipramine-like antidepressants (tricyclics), neuroleptics

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

Linked to perindopril

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

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (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 10 Plus**. 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 receptor antagonists, NSAID's, heparins, immunosuppressant medicines 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 10 Plus** 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 medicine.

Fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE-inhibitors/Renin angiotensin receptor blockers may precipitate acute kidney injury. 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

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 medicine.

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 supplements or potassium-containing salt substitutes

Hyperkalaemia (potentially lethal), especially in conjunction with renal impairment (additive hyperkalaemic effects). The combination of **Prexum 10 Plus** with the above-mentioned medicines is not recommended (see section 4.4).

If concomitant use is nonetheless indicated, they should be used with caution and with frequent monitoring of serum potassium. For use of spironolactone in heart failure, see section “Concomitant use which requires special care”.

Concomitant use which requires special care

Antidiabetic medicines (insulin, oral hypoglycaemic medicines)
Epidemiological studies have suggested that concomitant administration of ACE-inhibitors and antidiabetic medicines (insulins, oral hypoglycaemic medicines) 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.

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, the diuretic must be discontinued before initiating treatment.

In diuretic-treated congestive heart failure an ACE-inhibitor should be initiated at a very low dosage, possibly after reducing the dosage of the associated non-potassium-sparing diuretic.
In all cases, renal function (creatinine levels) must be monitored during the first few weeks of ACE-inhibitor therapy.

Potassium-sparing diuretics (eplerenone, spironolactone)
With eplerenone or spironolactone at doses between 12,5 mg to 50 mg by day and with low doses of ACE-inhibitors
Concomitant use of potassium sparing diuretics in patients with class II-IV heart failure (NYHA) with an ejection fraction < 40 %, and who have previously been treated with ACE-inhibitors and loop diuretics, have a high risk of hyperkalaemia, which may be fatal.
Before initiating **Prexum 10 Plus**, check the absence of hyperkalaemia and renal impairment.

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

Concomitant use which requires some care

Antihypertensive medicines and vasodilators

Concomitant use of these medicines may increase the hypotensive effects of perindopril as contained in **Prexum 10 Plus**. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Allopurinol, cytostatic or immunosuppressive medicines, systemic corticosteroids or procainamide

Concomitant administration with **Prexum 10 Plus** may lead to an increased risk for leucopenia.

Anaesthetic medicines

Prexum 10 Plus may enhance the hypotensive effects of certain anaesthetic medicines.

Sympathomimetics

Sympathomimetics may reduce the antihypertensive effects of ACE-inhibitors.

Gold

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

Linked to indapamide

Concomitant use which requires special care

***Torsades de pointe*s inducing medicines**

Due to the risk of hypokalaemia, indapamide should be administered with caution when associated with medicines that induce *torsades de pointes* such as:

- class IA antidysrhythmic medicines (quinidine, hydroquinidine, disopyramide).
- class III antidysrhythmic medicines (amiodarone, dofetilide, ibutilide, bretylium, sotalol); some neuroleptics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine),
- benzamides (amisulpride, sulpiride, sultopride, tiapride),
- butyrophenones (droperidol, haloperidol),
- other neuroleptics (pimozide),

- other substances (e.g., bepridil, cisapride, diphemanil, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, sparfloxacin, vincamine IV, methadone, astemizole, terfenadine).

Prevention of low potassium levels and correction if necessary, monitoring of the QT interval.

Potassium-lowering medicines Amphotericin B (IV route), glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives

Increased risk of low potassium levels (additive effect). Potassium levels should be monitored, and corrected, if necessary, in patients treated with cardiac glycosides. Non stimulant laxatives should be used.

Digoxin

Hypokalaemia and/or hypomagnesaemia predispose to the toxic effects of digitalis. Monitoring of plasma potassium, magnesium and ECG is recommended and, if necessary, adjusting the treatment.

Allopurinol

Concomitant treatment with indapamide may increase the incidence of hypersensitivity reactions to allopurinol.

Concomitant use which requires some care

Potassium-sparing diuretics (amiloride, spironolactone, triamterene)

Whilst rational combinations are useful in some patients, hypokalaemia or hyperkalaemia (particularly in patients with renal failure or diabetes) may still occur. Plasma potassium and ECG should be monitored and, if necessary, treatment reviewed.

Metformin

Lactic acidosis due to metformin caused by possible functional renal insufficiency linked to diuretics and in particular to loop diuretics. Do not use metformin when plasma creatinine levels exceed 135 micromol/l (15 mg/l) in men and 110 micromol/l (12 mg/l) in women.

Iodinated contrast medicine

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

Calcium (salts)

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

Ciclosporin, tacrolimus

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

Corticosteroids, tetracosactide (systemic route)

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Prexum 10 Plus is contraindicated during pregnancy (see section 4.3).

Pregnant women should be informed of the potential hazards to the foetus and must not take **Prexum 10 Plus** 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 10 Plus** 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, spina bifida) and of kidney malformations.

Prexum 10 Plus, passes through the placenta and can cause disturbances in foetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of **Prexum 10 Plus**, in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Indapamide

Prolonged exposure to thiazides or indapamide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a feto-placental ischaemia and growth retardation. Cases of hypoglycaemia and thrombocytopenia in neonates have been reported following exposure near term.

Lactation

Prexum 10 Plus is contraindicated during lactation.

Perindopril

It is not known whether perindopril is excreted into human breast milk.

Indapamide

There is insufficient information on the excretion of indapamide/metabolites in human milk. Indapamide is closely related to thiazide diuretics which have been associated with a decrease or suppression of milk lactation during breastfeeding. Hypersensitivity to sulphonamide-derived medicines and hypokalaemia might occur. Indapamide is contraindicated during breastfeeding.

Fertility

Reproductive toxicity studies showed no effect on fertility in female and male rats. No effects on human fertility are anticipated.

4.7 Effects on ability to drive and use machines

Reactions related to low blood pressure may occur in some patients, which may impair the ability to drive or operate machinery.

4.8 Undesirable effects

Summary of safety profile

The administration of perindopril inhibits the renin-angiotensin-aldosterone axis and tends to reduce the potassium loss caused by indapamide.

Six percent of the patients on treatment with **Prexum 10 Plus** experience hypokalaemia (potassium level < 3,4 mmol/l).

The most commonly reported adverse reactions with perindopril and indapamide given separately are:

- With perindopril: decreased appetite, dizziness, headache, paraesthesia, vertigo, dysgeusia, visual impairment, tinnitus, hypotension, cough, dyspnoea, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, vomiting, pruritus, rash, maculopapular rash, muscle cramps and asthenia.
- With indapamide: hypokalaemia, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

Tabulated list of adverse reactions

The following side effects have been observed during clinical trials and/or post marketing use 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.

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**	
		Perindopril	**Indapamide**
Infection and Infestations	Rhinitis	Very rare	-
Endocrine disorders	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Rare	-
Blood and Lymphatic System Disorders	Eosinophilia	Uncommon*	-
	Thrombocytopenia (see section 4.4))	Very rare	Very rare
	Leukopenia	Very rare	Very rare
	Neutropenia (see section 4.4)	Very rare	-
	Agranulocytosis (see section 4.4)	Very rare	Very rare
	Pancytopenia	Very rare	-
	Aplastic anaemia	-	Very rare
	Haemolytic anaemia (see section 4.4)	Very rare	Very rare
Immune system disorders	Hypersensitivity (reaction, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions.)	-	Common
Metabolism and Nutrition Disorders	Hypokalaemia	-	Common
	Hypoglycaemia (see sections 4.4 and 4.5)	Uncommon*	-
	Hyperkalaemia, reversible on discontinuation (see section 4.4)	Uncommon*	-
	Hyponatraemia (see section 4.4)	Uncommon*	Uncommon
	Hypochloraemia	-	Rare
	Hypomagnesaemia	-	Rare
	Hypercalcaemia	-	Very rare
Psychiatric Disorders	Depression	Uncommon*	-
	Altered mood	Uncommon	-
	Sleep disorder	Uncommon	-
	Confusion	Very rare	-
Nervous System Disorders	Dizziness	Common	-
	Headache	Common	Rare
	Paraesthesia	Common	Rare
	Dysgeusia	Common	-

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Perindopril	**Indapamide**
	Somnolence	Uncommon*	-
	Syncope	Uncommon*	Not known
	Stroke possibly to excessive hypotension in high-risk patients (see section 4.4)	Very rare	-
	Possibility of onset of hepatic encephalopathy in case of hepatic insufficiency (see section 4.4)	-	Not known
Eye Disorders	Visual impairment	Common	Not known
	Myopia (see section 4.4)	-	Not known
	Acute angle-closure glaucoma	-	Not known
	Blurred vision	-	Not known
	Choroidal effusion	-	Not known
Ear and Labyrinth Disorders	Vertigo	Common	Rare
	Tinnitus	Common	-
Cardiac Disorders	Palpitations	Uncommon*	-
	Tachycardia	Uncommon*	-
	Angina pectoris (see section 4.4)	Very rare	-
	Dysrhythmia (including bradycardia, ventricular tachycardia, atrial fibrillation)	Very rare	Very rare
	Myocardial infarction possibly secondary to excessive hypotension in high-risk patients (see section 4.4)	Very rare	-
	Torsades de pointes (potentially fatal) (see sections 4.4 and 4.5)	-	Not known
Vascular Disorders	Hypotension (and effects related to hypotension) (see section 4.4)	Common	Very rare
	Vasculitis	Uncommon*	-
	Flushing	Rare*	-
	Raynaud's phenomenon	Not known	
Respiratory, Thoracic and Mediastinal Disorders	Cough (see section 4.4)	Common	-
	Dyspnoea	Common	-
	Bronchospasm	Uncommon	-
	Eosinophilic pneumonia	Very rare	-
Gastro-intestinal Disorders	Abdominal pain	Common	-
	Constipation	Common	Rare
	Diarrhoea	Common	-
	Dyspepsia	Common	-
	Nausea	Common	Rare
	Vomiting	Common	Uncommon
	Dry mouth	Uncommon	Rare
	Pancreatitis	Very rare	Very rare

MedDRA System Organ Class	Undesirable Effects	Frequency	
		Perindopril	**Indapamide**
Hepato-biliary Disorders	Hepatitis (see section 4.4)	Very rare	Not known
	Hepatic function abnormal	-	Very rare
Skin and Subcutaneous Tissue Disorders	Pruritus	Common	-
	Rash	Common	-
	Maculo-papular rash	-	Common
	Urticaria (see section 4.4)	Uncommon	Very rare
	Angioedema (see section 4.4)	Uncommon	Very rare
	Purpura	-	Uncommon
	Hyperhidrosis	Uncommon	-
	Psoriasis aggravation	Rare*	-
	Photosensitivity reaction	Uncommon*	Not known
	Pemphigoid	Uncommon*	-
	Erythema multiforme	Very rare	-
	Toxic epidermal necrolysis	-	Very rare
	Stevens Johnson syndrome	-	Very rare
Musculoskeletal and Connective Tissue Disorders	Muscle cramps	Common	-
	Possible aggravation of pre-existing acute disseminated lupus erythematosus	-	Uncommon
	Arthralgia	Uncommon*	-
	Myalgia	Uncommon*	-
	Muscular weakness	-	Not known
	Rhabdomyolysis	-	Not known
Renal and Urinary Disorders	Renal failure	Uncommon	Rare
	Anuria/oliguria	Rare*	-
	Acute renal failure	Rare	-
Reproductive System and Breast disorders	Erectile dysfunction	Uncommon	Uncommon
General Disorders and Administration Site Condition	Asthenia	Common	-
	Chest pain	Uncommon*	-
	Malaise	Uncommon*	-
	Peripheral oedema	Uncommon*	-
	Pyrexia	Uncommon*	-
	Fatigue	-	Rare
Investigations	Increased blood urea	Uncommon*	-
	Increased blood creatinine	Uncommon*	-
	Increased blood bilirubin	Rare	-
	Increased hepatic enzyme	Rare	Not known
	Decreased haemoglobin and decreased haematocrit (see section 4.4)	Very rare	-

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**	
		Perindopril	**Indapamide**
	Increased blood glucose	-	Not known
	Increased blood uric acid	-	Not known
	Electrocardiogram QT prolonged (see sections 4.4 and 4.5)	-	Not known
Injury, Poisoning and procedural complications	Fall	Uncommon*	-

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

Description of selected adverse reactions:

During phase II and III studies comparing indapamide 1,5 mg and 2,5 mg, plasma potassium analysis showed a dose-dependent effect of indapamide:

- **Indapamide 1,5 mg**: Plasma potassium < 3,4 mmol/l was seen in 10 % of patients and < 3,2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0,23 mmol/l.
- **Indapamide 2,5 mg:** Plasma potassium < 3,4 mmol/l was seen in 25 % of patients and < 3,2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0,41 mmol/l.

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

The most likely adverse reaction in cases of overdose is hypotension, sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria which may progress to anuria (due to hypovolaemia). Salt and water disturbances (low sodium levels, low potassium levels) may occur.

Management

The first measures to be taken consist of rapidly eliminating the product(s) ingested by gastric lavage and/or administration of activated charcoal, then restoring fluid and electrolyte balance in a specialised centre until they return to normal. If marked hypotension occurs, this can be treated by placing the patient in a supine position with the head lowered. If necessary, an intravenous infusion of isotonic saline (0,9 % sodium chloride) may be given, or any other method of volaemic expansion may be used. Perindoprilat, the active form of perindopril, can be dialysed.

5. PHARMAOCOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: perindopril and diuretics, ATC code: C09BA04

Perindopril arginine 10 mg/indapamide 2,5 mg is a combination of perindopril arginine salt, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic.

Perindopril

Perindopril is an inhibitor of the angiotensin converting enzyme (ACE-inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; it reduces aldosterone secretion, increases plasma renin activity and reduces total peripheral resistance with a preferential action on the vascular bed in muscle and the kidney, with no accompanying salt and water retention or reflex tachycardia. Perindopril acts through its active metabolite, perindoprilat. The other metabolites are inactive.

Perindopril reduces the work of the heart

- by a vasodilatory effect on veins, probably caused by changes in the metabolism of prostaglandins reduction in pre-load,
- by reduction of the total peripheral resistance reduction in afterload.

Characteristics of antihypertensive action

The antihypertensive activity after a single dose is maximal at between 4 and 6 hours and lasts for 24 hours.

Indapamide

Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

5.2 Pharmacokinetic properties

The co-administration of perindopril and indapamide does not change their pharmacokinetic properties by comparison to separate administration.

Perindopril

Absorption and bioavailability

After oral administration, perindopril is completely absorbed, and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour.
As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril arginine should be administered orally in a single daily dose in the morning before a meal.

Distribution

The volume of distribution is approximately 0,2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20 %, principally to angiotensin converting enzyme, but is concentration dependent.

Biotransformation

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.

Elimination

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

Linearity/non-linearity

A linear relationship has been demonstrated between the dose of perindopril and its plasma exposure.

Special populations

Elderly

Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure.

Patients with renal impairment

As plasma exposure to perindoprilat (AUC) is significantly increased in patients with moderate renal impairment, dosage adjustment in renal insufficiency is desirable depending on the degree of impairment (creatinine clearance).

In case of dialysis

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

In patients with cirrhosis

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.

Indapamide

Absorption

Indapamide is well absorbed from the digestive tract. The peak plasma level is reached in humans approximately one hour after oral administration of the product.

Distribution

Plasma protein binding is 79 %.

Biotransformation and elimination

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

Patients with renal impairment

The pharmacokinetics are unchanged in patients with renal insufficiency.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other excipients are:

Tablet core: lactose monohydrate, magnesium stearate (E470B), maltodextrin, silica colloidal anhydrous (E551), sodium starch glycolate (type A).

Tablet film-coating: glycerol (E422), hypromellose (E464), macrogol 6 000, magnesium stearate (E470B), titanium dioxide (E171, CI 77891).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 ºC.

Keep out of reach children.

Keep the bottle well closed to protect the tablets from moisture.

6.5 Nature and contents of container

White polypropylene tube equipped with a polyethylene flow reducer containing 30 tablets and a white polyethylene stopper containing white desiccant gel.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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