APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

PROPRIETARY NAME (and dosage form)

REPREX 2 mg (Tablets)

REPREX 4 mg (Tablets)

REPREX 8 mg (Tablets)

COMPOSITION:

REPREX 2 mg:

Each uncoated tablet contains perindopril tert-butylamine 2 mg. Contains lactose.

REPREX 4 mg :

Each uncoated tablet contains perindopril tert-butylamine 4 mg. Contains lactose.

REPREX 8 mg:

Each uncoated tablet contains perindopril tert-butylamine 8 mg. Contains lactose.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Vascular medicines- other hypotensives.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Perindopril is a specific, non-sulphydryl competitive angiotensin-1 converting enzyme (ACE) inhibitor.

It inhibits the conversion of relatively inactive angiotensin I to the active angiotensin II. Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone. Decreased angiotensin II levels result in a decrease in vasopressor activity and a reduction in aldosterone secretion, which may result in small increases in serum potassium. It is also thought that ACE – inhibition may inhibit degradation of bradykinin leading to increased bradykinin levels.

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

Pharmacokinetics:

Following oral administration the absorption of perindopril is rapid (peak concentration within 1 hour), and relatively complete (plasma-availability above 75 %). The peak concentration of the active metabolite, perindoprilat, is reached within 3 to 4 hours and peak pharmacological activity is obtained within 4 to 6 hours. In terms of trough versus peak blood pressure effect, the trough effect ranges between 75 –100 % of peak effect. Both perindopril and perindoprilat have a low volume of distribution and plasma protein binding is low. Perindoprilat binds to angiotensin converting enzyme at both tissue and plasma levels.
Apart from the active perindoprilat, perindopril gives rise to 5 metabolites all of which are inactive. Perindopril is eliminated in the urine and the half-life of its free fraction is approximately one hour. Breakdown of the bond between perindoprilat and the angiotensin converting enzyme leads to a pharmacodynamic half-life of about 25 hours. In the elderly, as well as in patients with cardiac failure or renal failure, the elimination of perindoprilat is slower. In such patients dosage adjustment should be applied in relation to the degree of reduction in creatinine clearance.
Reduction in blood pressure in patients treated with perindopril was accompanied by a reduction in peripheral resistance with no significant changes in glomerular filtration rate or heart rate. An increase in the compliance of large arteries was also observed, suggesting a direct effect on arterial smooth muscle, consistent with the results of animal studies.

INDICATIONS:

REPREX tablets are indicated in:

- Mild to moderate hypertension.
- Congestive heart failure not adequately controlled by conventional therapy with diuretics and digitalis and in whom vasodilatation is indicated.

CONTRA-INDICATIONS:

REPREX tablets are contra-indicated in:

- Sensitivity to any of the components of **REPREX**
- 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.
- Hereditary or idiopathic angioedema

- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria
- Thiazide diuretics in (fixed dose) combination with **REPREX** should not be given to patients with Addison's disease. This therapy is contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.
- Lithium therapy: Concomitant administration with **REPREX** may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see **WARNINGS AND SPECIAL PRECAUTIONS** and **PREGNANCY AND LACTATION**).
- Children: The safety of **REPREX** in children has not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

Should a woman become pregnant while receiving REPREX, the treatment should be stopped promptly and switched to a different class of medicine. Should a woman contemplate pregnancy, the doctor should consider alternate medication.
(See "Contra-indications" and "Pregnancy and lactation").

Hypotension:

ACE-inhibitors, as in **REPREX** 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. 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. 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 **REPREX.** If hypotension becomes symptomatic, a reduction of the dose or discontinuation of **REPREX** may be necessary.

Aortic and mitral valve stenosis/hypertrophic cardiomyopathy:

REPREX 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 (see **CONTRA-INDICATIONS**).

Impaired renal function:

In cases of renal impairment (creatinine clearance < 60 ml/min) the initial **REPREX** dosage should be adjusted according to the patient's creatinine clearance and then as a function of the patient's response to treatment (see **Renal insufficiency**). 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, as in **REPREX** 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, as in **REPREX** increases in blood urea and serum creatinine may occur (see **CONTRA-INDICATIONS**). 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 **REPREX** therapy.

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

In acute myocardial infarction, treatment with **REPREX** should not be initiated in patients with evidence of renal dysfunction (serum creatinine concentrations exceeding 177 micromol/l or proteinuria exceeding 500 mg/24 hours). If renal dysfunction develops during treatment (serum creatinine concentrations exceeding 177 micromol/l or doubling of the pre-treatment value) then **REPREX** may need to be withdrawn (see also **CONTRA-INDICATIONS**).

In acute myocardial infarction, patients may develop persistent hypotension and/or impaired renal function.

Haemodialysis patients:

Anaphylactic reactions have been reported in patients dialysed with high flux membranes, and treated concomitantly with an ACE-inhibitor, as in **REPREX**. 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 **REPREX** in patients with a recent kidney transplant.

Hypersensitivity/angioedema:

Angioedema of the face, lips, mucous membranes, tongue, glottis and/or larynx, and extremities has been reported, in patients treated with **REPREX** (see **CONTRA-INDICATIONS**). This may occur at any time during therapy. In such cases, **REPREX** 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 as with **REPREX** may be at increased risk of angioedema while receiving an ACE-inhibitor.

Anaphylactic reactions during low-density lipoproteins (LDL) apheresis:

Patients receiving ACE-inhibitors as in **REPREX** 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.

Anaphylactic reactions during desensitisation:

Patients receiving ACE-inhibitors as in **REPREX** 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:

REPREX has 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 **REPREX** and receive appropriate medical follow-up.

Neutropenia/agranulocytosis/thrombocytopenia/anaemia:

Neutropenia, agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE-inhibitors as in **REPREX**. In patients with normal renal function and no other complicating factors, neutropenia rarely occurs.

REPREX 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 **REPREX** 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.

Race:

REPREX causes a higher rate of angioedema in black patients than in other ethnic groups. **REPREX** 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, as in **REPREX.** Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. **REPREX** 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, **REPREX** 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 **REPREX**. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, uncontrolled diabetes mellitus, or those using concomitant potassium-sparing diuretics (see **CONTRA-INDICATIONS**), potassium supplements or potassium-containing salt substitutes; or those patients taking other medicines associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed necessary, regular monitoring of serum potassium is recommended.

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 **REPREX** (see **INTERACTIONS**).

Lithium:

The combination of lithium and **REPREX** is generally not recommended (see **CONTRA-INDICATIONS** and **INTERACTIONS**).

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

The combination of **REPREX** and potassium sparing diuretics (see **CONTRA-INDICATIONS**), potassium supplements or potassium-containing salt substitutes is generally not recommended (see **INTERACTIONS**).

Special Precautions:

Clinical laboratory test findings:

At the start of treatment, a fall in haemoglobin may occur. A rise in plasma potassium has been reported.

Special populations:

Dosage should be adjusted in the elderly and in patients with renal insufficiency. (see DOSAGE AND DIRECTIONS FOR USE).

REPREX contains lactose and should not be given to patients with rare hereditary problems, or a history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Driving and using machinery:

Caution when driving or performing tasks requiring alertness because of possible dizziness.

INTERACTIONS:

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 **REPREX**. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, and by increasing volume or salt intake prior to initiating therapy with low and increasing doses of perindopril.

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes, other medicines that can cause hyperkalaemia:

Hyperkalaemia may occur in some patients treated with **REPREX**. Potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride) (see **CONTRA-INDICATIONS**), potassium supplements or potassium-containing salt substitutes, may lead to significant increases in serum potassium. Therefore, the combination of **REPREX** with the above-mentioned medicines is not recommended. If concomitant use is indicated because of confirmed hypokalaemia, they should be used with caution and serum potassium should frequently be monitored.

An additive hyperkalaemic effect is possible in patients receiving ACE-inhibitors, as in **REPREX** with other medicines that can cause hyperkalaemia (such as ciclosporin), and serum potassium concentrations should be monitored.

Lithium:

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with **REPREX.** 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 **REPREX** with lithium is not recommended (see **CONTRA-INDICATIONS**), but if the combination proves necessary, careful monitoring of serum lithium levels should be performed.

Non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin ≥ 3 g/day:

The administration of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the antihypertensive effect of **REPREX**. 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.

Antihypertensive agents and vasodilators:

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

Antidiabetic agents:

Epidemiological studies have suggested that concomitant administration of ACE-inhibitors, as in **REPREX** 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.

Acetylsalicylic acid, thrombolytics, beta-blockers and nitrates:

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

Tricyclic antidepressants/antipsychotics/anaesthetics:

Concomitant use of certain anaesthetic medicines, tricyclic antidepressants and antipsychotics with **REPREX** may result in further reduction of blood pressure.

Sympathomimetics:

Sympathomimetics may reduce the antihypertensive effects of **REPREX**.

PREGNANCY AND LACTATION:

Pregnancy:

REPREX is contra-indicated during pregnancy and lactation.

REPREX passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns have been

reported after administration of **REPREX** in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.

In addition, use of **REPREX** during the first trimester of pregnancy has been associated with an increased risk of birth defects, in particular of the cardiovascular and the central nervous system (see **CONTRA-INDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

Lactation:

The safety of REPREX during lactation has not been established and therefore mothers on REPREX should not breastfeed their babies.

DOSAGE AND DIRECTIONS FOR USE:

Mild to moderate hypertension:

The tablets should be taken before meals.

The recommended dosage is 4 mg orally taken in the morning before breakfast which can be increased to a single dose of 8 mg if necessary after one month of treatment.

In elderly patients and in cardiac failure substantially lower dosage should be used because of impaired clearance.

Insulin and non-insulin dependent diabetics can be treated with the usual doses.

Congestive heart failure:

The treatment should be initiated under close medical supervision. Initial dose of 2 mg orally as a single dose in the morning which may, in most instances, be increased to 4 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 hypovolemia may occur, the diuretic therapy should be discontinued prior to initiation of therapy with **REPREX**. In the case of combination with a diuretic it is not advisable to prescribe a potassium salt or a potassium sparing agent before assay of blood potassium, and attention should be paid to possible overdosage of the diuretic (see Contra-indications and Interactions).

Renal insufficiency:

In patients with renal insuffiency (creatinine clearance 30 – 60 ml/min), the dosage of perindopril must be adjusted in relation to the severity of the insufficiency. The following dosages may be recommended:

Creatinine clearance	Recommended dosage
Between 30 and 60 ml/min	2 mg per day

REPREX is contra-indicated in patients with a creatinine clearance below 30 ml/min.

Perindopril is dialysable (70 ml/min).

SIDE-EFFECTS:

Blood and lymphatic system disorders:

Less frequent:

Decreases in haemoglobin, haematocrit, thrombocytopenia, leucopenia/neutropenia, agranulocytosis, pancytopenia. Cases in patients with a congenital deficiency of G-6PDH, of haemolytic anaemia are rarely reported.

Anaemias.

Psychiatric disorders:

Less frequent:

Mood and/or sleep disturbances.

Nervous system disorders:

Frequent:

Headache, dizziness, vertigo, paraesthesia.

Less frequent

Confusion.

Eye disorders:

Frequent:

Visual disturbances.

Ear and labyrinth disorders:

Frequent:

Tinnitus.

Cardio-vascular disorders:

Frequent:

Hypotension and effects related to hypotension.

Less frequent:

Dysrhythmia, angina pectoris, myocardial infarction and stroke, possibly secondary to excessive hypotension in high-risk patients e.g. in patients with ischaemic heart disease or cerebrovascular disease.

The following side-effects have been reported and frequencies are unknown:

Orthostatic effects (including hypotension), palpitations.

Respiratory, thoracic and mediastinal disorders:

Frequent:

Cough and dyspnoea.

Less frequent:

Bronchospasm, eosinophilic pneumonia and rhinitis.

Gastro-intestinal disorders:

Frequent:

Unspecific digestive disorders, nausea, vomiting, abdominal pain, taste disturbance, dyspepsia, diarrhoea and constipation.

Less frequent:

Pancreatitis, dry mouth.

Hepato-biliary disorders:

Less frequent:

Hepatocellular injury or cholestatic jaundice, hepatitis either cytolytic or cholestatic.

Skin and subcutaneous tissue disorders:

Frequent:

Rash and pruritus.

Less frequent:

Angioedema of face, lips, mucous membranes, tongue, glottis and/or larynx, extremities and urticaria, erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Frequent:

Muscular cramps.

Renal and urinary disorders:

Less frequent:

Renal insufficiency, acute renal failure.

Reproductive system and breast disorders:

Less frequent:

Impotence.

General disorders:

Frequent:

Asthenia.

Less frequent:

Sweating.

Investigations:

Less frequent:

Elevation of liver enzymes and serum bilirubin.

The following side-effects have been reported and frequencies are unknown:

In the presence of renal insufficiency, severe heart failure and renovascular hypertension, there may be an increase in blood urea, plasma creatinine and hyperkalaemia, but it is reversible on discontinuation of the medication.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms associated with overdose of **REPREX** 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. **REPREX** 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.

IDENTIFICATION:

REPREX 2 mg

White to off-white coloured round biconvex uncoated tablets, with debossing “D” on one side and “57” on other side.

REPREX 4 mg

White to off-white coloured capsule shaped uncoated tablets, with debossing “D” on one side and “5” & “8” on either side of the breakline on another side.

REPREX 8 mg

White to off-white coloured round biconvex uncoated tablets, with debossing “D” on one side and “5” & “9” on either side of breakline on another side.

PRESENTATION:

REPREX 2 mg, REPREX 4 mg, and REPREX 8 mg:

Blister Packs:

Tablets are packed in blister packs (composed of clear PVC film and silver coloured aluminium lidding foil).

Each blister contains 10 tablets. Three blisters are packed in a bag together with a silica gel sachet.

Pack size 30’s: Each carton contains 3 blisters of 10 tablets each.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in a dry place.

Do not remove the blisters from the carton until required.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

REPREX 2 mg: 43/7.1.3/1032

REPREX 4 mg: 43/7.1.3/1033

REPREX 8 mg: 43/7.1.3/1034

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration:

30 September 2011

Date of revision:

18 September 2021