

Captopril

Core Safety Profile

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients or to any other ACE inhibitor.

History of angioedema associated with previous ACE inhibitor therapy.

Hereditary/idiopathic angioneurotic oedema.

Second and third trimesters of pregnancy.

4.4 Special warnings and precautions for use

Hypotension: rarely hypotension is observed in uncomplicated hypertensive patients.

Symptomatic hypotension is more likely to occur in hypertensive patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, vomiting, or haemodialysis. Volume and/or sodium depletion should be corrected before the administration of an ACE inhibitor and a lower starting dose should be considered. As with any antihypertensive agent, excessive blood pressure lowering in patients with ischaemic cardiovascular or cerebrovascular disease may increase the risk of myocardial infarction or stroke. If hypotension develops, the patient should be placed in a supine position. Volume repletion with intravenous normal saline may be required.

Renovascular hypertension: there is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

Angioedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including Captopril. This may occur at any time during treatment. In such cases, Captopril should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in

relieving symptoms. Angioneurotic oedema associated with laryngeal edema 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 solution 1:1000 (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 (see 4.3). Intestinal angioedema has been reported rarely in patients

treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain (see 4.8).

Cough: cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy.

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

Hyperkalaemia: elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended.

Aortic and mitral valve stenosis/Obstructive hypertrophic cardiomyopathy/Cardiogenic shock: ACE inhibitors should be used with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and hemodynamically significant obstruction.

Neutropenia/Agranulocytosis: neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors, including captopril. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Captopril 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 captopril is used in such patients, it is advised that white blood cell count and differential counts should be performed prior to therapy, every 2 weeks during the first 3 months of captopril therapy, and periodically thereafter. During treatment all patients should be instructed to report any sign of infection (e.g. sore throat, fever) when a differential white blood cell count should be performed.

Captopril and other concomitant medication (see 4.5) should be withdrawn if neutropenia (neutrophils less than 1000/mm³) is detected or suspected.

In most patients neutrophil counts rapidly return to normal upon discontinuing captopril.

Proteinuria: proteinuria may occur particularly in patients with existing renal function impairment or on relatively high doses of ACE inhibitors.

Total urinary proteins greater than 1 g per day were seen in about 0.7% of patients receiving captopril.

The majority of patients had evidence of prior renal disease or had received relatively high doses of captopril (in excess of 150 mg/day), or both. Nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Patients with prior renal disease should have urinary protein estimations (dip-stick on first morningurine) prior to treatment, and periodically thereafter.

Anaphylactoid reactions during desensitisation: sustained life-threatening anaphylactoid reactions have been rarely reported for patients undergoing desensitising treatment with hymenoptera venom while receiving another ACE inhibitor. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge.

Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Anaphylactoid reactions during high-flux dialysis/lipoprotein apheresis membrane exposure:

anaphylactoid reactions have been reported in patients haemodialysed with high-flux dialysis membranes or undergoing low-density lipoprotein apheresis with dextran sulphate absorption. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication.

Surgery/Anaesthesia: hypotension may occur in patients undergoing major surgery or during treatment with anaesthetic agents that are known to lower blood pressure. If hypotension occurs, it may be corrected by volume expansion.

Diabetic patients: the glycaemia levels should be closely monitored in diabetic patients previously treated with oral antidiabetic drugs or insulin, namely during the first month of treatment with an ACE inhibitor.

Risk of hypokalaemia: the combination of an ACE inhibitor with a thiazide diuretic does not rule out the occurrence of hypokalaemia. Regular monitoring of kalaemia should be performed.

Combination with lithium: INVENTED NAME is not recommended in association with lithium due to the potentiation of lithium toxicity (see 4.5).

Ethnic differences: As with other angiotensin converting enzyme inhibitors, INVENTED NAME is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Pregnancy: ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with ACE inhibitors should be stopped

immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Lactose: INVENTED NAME contains lactose and therefore should not be used in cases of congenital galactosaemia and malabsorption of glucose and galactose or in lactase-deficient syndromes (rare metabolic diseases).

4.5 Interaction with other medicinal products and other forms of interaction

Potassium sparing diuretics or potassium supplements:

ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalaemia they should be used with caution and with frequent monitoring of serum potassium (see 4.4).

Diuretics (thiazide or loop diuretics): prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with captopril (see 4.4). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of captopril. However, no clinically significant drug interactions have been found in specific studies with hydrochlorothiazide or furosemide.

Other antihypertensive agents: captopril has been safely co administered with other commonly used antihypertensive agents (e.g. beta-blockers and long-acting calcium channel blockers). Concomitant use of these agents may increase the hypotensive effects of captopril. Treatment with nitroglycerine and other nitrates, or other vasodilators, should be used with caution.

Alpha blocking agents: concomitant use of alpha blocking agents may increase the antihypertensive effects of captopril and increase the risk of orthostatic hypotension.

Treatments of acute myocardial infarction: captopril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates in patients with myocardial infarction.

Tricyclic antidepressants/Antipsychotics: ACE inhibitors may enhance the hypotensive effects of certain tricyclic antidepressants and antipsychotics (see 4.4). Postural hypotension may occur.

Allopurinol, procainamide, cytostatic or immunosuppressive agents: concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia especially when the latter are used at higher than currently recommended doses.

Sympathomimetics: may reduce the antihypertensive effects of ACE inhibitors; patients should be carefully monitored.

Antidiabetics: pharmacological studies have shown that ACE inhibitors, including captopril, can potentiate the blood glucose-reducing effects of insulin and oral antidiabetics such as sulphonylurea in diabetics. Should this very rare interaction occur, it may be necessary to reduce the dose of the antidiabetic during simultaneous treatment with ACE inhibitors.

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. The combination of captopril with lithium is therefore not recommended and careful monitoring of serum lithium levels should be performed if the combination proves necessary.

Non-steroidal anti-inflammatory medicinal products: it has been described that non-steroidal antiinflammatory medicinal products (NSAIDs) and ACE inhibitors exert an additive effect on the increase in serum potassium, whereas renal function may decrease. These effects are, in principle, reversible. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated. Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor.

Clinical Chemistry

Captopril may cause a false-positive urine test for acetone.

4.6 Pregnancy and lactation

Pregnancy:

Given the effects of the individual components in this combination product on pregnancy, the use of INVENTED NAME is not recommended during the first trimester of pregnancy (see 4.4). The use of INVENTED NAME is contra-indicated during the 2nd and 3rd trimester of pregnancy (see 4.3 and 4.4).

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

Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Should exposure to ACE inhibitors 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 4.3 and 4.4).

Lactation:

Limited pharmacokinetic data demonstrate very low concentrations in breast milk. Although these concentrations seem to be clinically irrelevant, the use of INVENTED NAME in breastfeeding is not recommended for preterm infants and for the first few weeks after delivery, because of the hypothetical risk of cardiovascular and renal effects and because there is not enough clinical experience.

In the case of an older infant, the use of INVENTED NAME in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

4.7 Effects on ability to drive and use machines

As with other antihypertensives, the ability to drive and use machines may be reduced, e.g. at the start of the treatment or when the dose is modified, and also when used in combination with alcohol, but these effects depend on the individual's susceptibility.

4.8 Undesirable effects

Frequency is defined using the following convention: common ($> 1/100$, $< 1/10$), uncommon ($> 1/1,000$, $< 1/100$), rare ($> 1/10,000$, $< 1/1,000$) and very rare ($< 1/10,000$).

Undesirable effects reported for captopril and/or ACE inhibitor therapy include:

Blood and lymphatic system disorders:

Very rare: neutropenia/agranulocytosis (see 4.4), pancytopenia particularly in patients with renal dysfunction (see 4.4), anaemia (including aplastic and haemolytic), thrombocytopenia, lymphadenopathy, eosinophilia, autoimmune diseases and/or positive ANA-titres.

Metabolism and nutrition disorders:

Rare: anorexia

Very rare: hyperkalaemia, hypoglycaemia (see 4.4)

Psychiatric disorders:

Common: sleep disorders

Very rare: confusion, depression.

Nervous system disorders:

Common: taste impairment, dizziness.

Rare: drowsiness, headache and paraesthesia.

Very rare: cerebrovascular incidents, including stroke, and syncope.

Eye disorders:

Very rare: blurred vision.

Cardiac disorders:

Uncommon: tachycardia or tachyarrhythmia, angina pectoris, palpitations.

Very rare: cardiac arrest, cardiogenic shock.

Vascular disorders:

Uncommon: hypotension (see 4.4), Raynaud syndrome, flush, pallor.

Respiratory, thoracic and mediastinal disorders:

Common: dry, irritating (non-productive) cough (see 4.4) and dyspnoea.

Very rare: bronchospasm, rhinitis, allergic alveolitis/eosinophilic pneumonia.

Gastrointestinal disorders:

Common: nausea, vomiting, gastric irritations, abdominal pain, diarrhoea, constipation, dry mouth.

Rare: stomatitis/aphthous ulcerations, intestinal angioedema (see 4.4).

Very rare: glossitis, peptic ulcer, pancreatitis.

Hepatobiliary disorders:

Very rare: impaired hepatic function and cholestasis (including jaundice), hepatitis including necrosis, elevated liver enzymes and bilirubin.

Skin and subcutaneous tissue disorders:

Common: pruritus with or without a rash, rash, and alopecia.

Uncommon: angioedema (see 4.4).

Very rare: urticaria, Stevens Johnson syndrome, erythema multiforme, photo sensitivity, erythroderma, pemphigoid reactions and exfoliative dermatitis.

Musculoskeletal and connective tissue disorders:

Very rare: myalgia, arthralgia.

Renal and urinary disorders:

Rare: renal function disorders including renal failure, polyuria, oliguria, increased urine frequency

Very rare: nephrotic syndrome.

Reproductive system and breast disorders:

Very rare: impotence, gynaecomastia.

General disorders and administration site conditions:

Uncommon: chest pain, fatigue, malaise

Very rare: fever.

Investigations:

Very rare: proteinuria, eosinophilia, increase of serum potassium, decrease of serum sodium, elevation of BUN, serum creatinine and serum bilirubin, decreases in haemoglobin, haematocrit, leucocytes, thrombocytes, positive ANA-titre, elevated ESR.

4.9 Overdose

Symptoms of overdosage are severe hypotension, shock, stupor, bradycardia, electrolyte disturbances and renal failure.

Measures to prevent absorption (e.g. gastric lavage, administration of adsorbents and sodium sulphate within 30 minutes after intake) and hasten elimination should be applied if ingestion is recent. If hypotension occurs, the patient should be placed in the shock position and salt and volume supplementations should be given rapidly. Treatment with angiotensin-II should be considered. Bradycardia or extensive vagal reactions should be treated by administering atropine. The use of a pacemaker may be considered. Captopril may be removed from circulation by haemodialysis.