SUMMARY OF THE PRODUCT CHARACTERISTICS

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

1. NAME OF THE MEDICINAL PRODUCT

Quinapril/Hydrochlorothiazide Actavis 10/12.5 mg film-coated tablets
Quinapril/Hydrochlorothiazide Actavis 20/12.5 mg film-coated tablets
Quinapril/Hydrochlorothiazide Actavis 20/25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Quinapril/Hydrochlorothiazide Actavis 10/12.5 mg
Each tablet contains quinapril hydrochloride equivalent to 10 mg quinapril and 12.5 mg hydrochlorothiazide.

Quinapril/Hydrochlorothiazide Actavis 20/12.5 mg
Each tablet contains quinapril hydrochloride equivalent to 20 mg quinapril and 12.5 mg hydrochlorothiazide.

Quinapril/Hydrochlorothiazide Actavis 20/25 mg
Each tablet contains quinapril hydrochloride equivalent to 20 mg quinapril and 25 mg hydrochlorothiazide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Quinapril/Hydrochlorothiazide Actavis 10/12.5 mg:
Oval, pink, biconvex tablet with score line on both sides and marked with "I" on one side. Size 4.5 x 8.7 mm.

Quinapril/Hydrochlorothiazide Actavis 20/12.5 mg:
Oval, pink, biconvex tablet with score line on both sides and marked with "I" on one side. Size 5.8 x 11.3 mm.

Quinapril/Hydrochlorothiazide Actavis 20/25 mg:
Round, pink, biconvex tablet with break score on both sides and marked with "I" on one side. Diameter 8.5 mm.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in those patients where a combined treatment with quinapril and a diuretic agent is appropriate.

4.2 Posology and method of administration

Posology

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

Dose titration of the individual components is recommended before administration of the fixed combination. When clinically appropriate, a direct change from monotherapy to a fixed combination may be considered.

The usual maintenance dose is 10 mg quinapril and 12.5 mg hydrochlorothiazide once daily in the morning. The dose may be increased at intervals of at least 3 weeks. The maximum dose is 20 mg quinapril and 25 mg hydrochlorothiazide.

Previous diuretic therapy
Symptomatic hypotension may occur after the initial dose of the fixed combination; this is more likely in patients who are volume and/or salt depleted as a result of previous diuretic therapy. In such patients diuretic therapy should be discontinued 2 to 3 days prior to initiation of therapy with the fixed combination. If this is not possible, treatment should be initiated with a 5 mg dose of quinapril alone.

Renal impairment
In patients with a creatinine clearance between 30 and 60 ml/min the individual doses of the single components should be titrated with special care before changing to the fixed combination.
The dose of the fixed combination should be kept as low as possible.

The fixed combination is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min), see section 4.3.

Elderly patients
In elderly patients the individual doses of the single components should be titrated with special care before changing to the fixed combination.
The dose of the fixed combination should be kept as low as possible.

Paediatric population
Efficacy and safety of use in children and adolescents has not been established. Use in children and adolescents is therefore not recommended.

Method of administration

The tablets should be taken with a sufficient amount of liquid, and can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance, to any other ACE inhibitor, or to any of the excipients listed in section 6.1.
- Hypersensitivity to hydrochlorothiazide or other sulphonamide-derivatives.
- History of angioedema associated with previous ACE inhibitor therapy.
- Hereditary or idiopathic angioneurotic oedema.
- Anuria or severe renal impairment (creatinine clearance < 30 ml/min).
- Severe hepatic impairment.
- Dynamic left ventricular outflow obstruction
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6)
- The concomitant use of Quinapril/Hydrochlorothiazide Actavis with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2) (see sections 4.5 and 5.1).

4.4 Special warnings and special precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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).

Sensitivity reactions
Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma, e.g., purpura, photosensitivity, urticaria, necrotising angiitis, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions.

Hypotension
Quinapril/hydrochlorothiazide can cause symptomatic hypotension, usually not more frequently than either drug as monotherapy. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving quinapril, hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or has severe renin-dependent hypertension (see section 4.5 and section 4.8).

Quinapril/hydrochlorothiazide should be used cautiously in patients receiving concomitant therapy with other antihypertensive agents. The thiazide component of quinapril/hydrochlorothiazide may potentiate the action of other antihypertensive drugs, especially ganglionic or peripheral adrenergic-blocking drugs. The antihypertensive effects of the thiazide component may also be enhanced in postsympathectomized patients.

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given without difficulty once the blood pressure has increased after volume expansion. However lower doses of quinapril or of any concomitant diuretic therapy should be considered if this event occurs.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy for hypertension may cause an excessive drop in blood pressure, which may be associated with oliguria, azotemia, and in rare instances, with acute renal failure and death in such patients. 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. Quinapril/ hydrochlorothiazide therapy should be started under close medical supervision. Patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased. Monitoring of kidney function and potassium levels should be performed. 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.

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

Heart Failure / Heart Disease
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

quinapril may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

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

Aortic and mitral valve stenosis / Hypertrophic cardiomyopathy
As with other ACE inhibitors, quinapril 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. In haemodynamically relevant cases the fixed combination should not be administered.

Renal disease
Quinapril/hydrochlorothiazide should be used with caution in patients with renal disease. In severe renal disease thiazides may precipitate azotemia and in moderate renal impairment (creatinine clearance 10-20 ml/min) thiazides are generally ineffective in such patients, and the effects of repeated dosing may be cumulative. If progressive renal impairment becomes evident, as indicated by increasing non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy (see section 4.3).

There is insufficient experience in patients with severe renal impairment (creatinine clearance <10 ml/min). Before ACE inhibitor treatment, renal artery stenosis should be excluded in renal transplant patients.

The half-life of quinaprilat is prolonged as creatinine clearance falls. Patients with a creatinine clearance of <60 mL/min require a lower initial dosage of quinapril (see section 4.2). These patients' dosage should be titrated upwards based upon therapeutic response, and renal function should be closely monitored although initial studies do not indicate that quinapril produces further deterioration in renal function. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.
In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. This is especially likely in patients with renal insufficiency. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. 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 quinapril therapy.

Some patients with hypertension or heart failure with no apparent pre-existing renal disease have developed increases (> 1.25 times the upper limit of normal) in blood urea nitrogen and serum creatinine, usually minor and transient, especially when quinapril has been given concomitantly with a diuretic. Increases in blood urea nitrogen and serum creatinine have been observed in 2 % and 2 % respectively of hypertensive patients on quinapril monotherapy and in 4 % and 3 %, respectively of hypertensive patients on quinapril/ hydrochlorothiazide. These increases are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or quinapril may be required.

Kidney transplantation
There is no experience regarding the administration of quinapril in patients with a recent kidney transplantation. Treatment with quinapril is therefore not recommended.

Impaired hepatic function
Quinapril/hydrochlorothiazide should be used with caution in patients with impaired hepatic function

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

or progressive liver disease, since minor alterations of fluid and electrolyte balance may result from thiazide treatment and may precipitate hepatic coma. Quinapril is rapidly deesterified to quinaprilat, (quinapril diacid, the principal metabolite), which, in human and animal studies, is a potent angiotensin-converting enzyme inhibitor. The metabolism of quinapril is normally dependent upon hepatic esterase. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril.

Rarely, ACE inhibitors have been associated with a syndrome beginning as a cholestatic jaundice and progressing to a fulminant hepatic necrosis (in some cases fatal). The mechanism of this syndrome is not understood. Patients who during ACE inhibitor therapy experience jaundice or clearly elevated hepatic enzymes should discontinue Quinapril/hydrochlorothiazide and receive appropriate medical follow-up.

Immune-mediated drug reactions / Anaphylactoid reactions
Desensitisation: Patients receiving ACE inhibitors during desensitising treatment with hymenoptera venom have sustained life-threatening anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld, but they have reappeared upon inadvertent re-challenge.

Stevens-Johnson syndrome and exacerbations or activation of systemic lupus erythematosus have been reported with thiazides.

Angioedema
Angioedema has been reported in patients treated with angiotensin-converting enzyme inhibitors. If laryngeal stridor or angioedema of the face, tongue, or glottis occur, treatment should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. Angioedema associated with laryngeal involvement may be fatal. Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction appropriate therapy e.g., subcutaneous adrenaline solution 1:1000 (0.3 to 0.5 ml) should be promptly administered. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

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

Intestinal angioedema
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 history of 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.

Ethnic differences
Black patients receiving ACE inhibitor therapy have been reported to have a higher incidence of angioedema compared to non-black patients. It should also be noted that in controlled clinical trials, ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks.

Haemodialysis and LDL Apheresis
Patients haemodialysed using high flux polyacrylonitrile (‘AN69’) membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for haemodialysis. Similar reactions have been observed during low density lipoprotein apheresis with dextran-sulphate. This method should therefore not be used in patients treated with ACE inhibitors.

Derangements of Serum Electrolytes

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

Patients receiving quinapril/hydrochlorothiazide should be observed for clinical signs of thiazide induced fluid or electrolyte imbalance. In such patients periodic determination of serum electrolytes (sodium and potassium in particular) should be performed. Because quinapril reduces the production of aldosterone, its combination with hydrochlorothiazide may minimise diuretic induced hypokalaemia.

The opposite effects of quinapril and hydrochlorothiazide on serum potassium will approximately balance each other in many patients so that no net effect upon serum potassium will be seen. In other patients, one or the other effect may be dominant and some patients may still require potassium supplements. Initial and periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Calcium excretion is decreased by thiazides. In a few patients on prolonged thiazide therapy, pathological changes in the parathyroid gland have been observed, with hypercalcemia and hypophosphatemia. More serious complications of hyperparathyroidism (renal lithiasis, bone resorption, and peptic ulceration) have not been seen.

Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficiency is generally mild and usually does not require treatment.
Thiazides should be discontinued before performing tests for parathyroid function.
Thiazides increase the urinary excretion of magnesium, and hypomagnesaemia may result. (See section 4.5).

Other Metabolic Disturbances
Thiazide diuretics tend to reduce glucose tolerance and raise serum levels of cholesterol, triglycerides, and uric acid. These effects are usually minor, but frank gout or overt diabetes may be precipitated in susceptible patients.

Hypokalemia
Conversely, treatment with thiazide diuretics has been associated with hypokalaemia, hyponatremia, and hypochloremic alkalosis. These disturbances have sometimes been manifest as one or more of the following: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, confusion, seizures and vomiting. Hypokalaemia can also sensitize or exaggerate the response of the heart to the toxic effects of digitalis. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or adrenocorticotrophic hormone (ACTH) (see section 4.5).

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including quinapril. 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 medicinal products associated with increases in serum potassium (e.g. heparin). Concomitant medications that could raise serum potassium levels should be carefully considered. Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician. If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Hypoglycaemia and Diabetes
In diabetic patients ACE inhibitors may enhance insulin sensitivity and have been associated with hypoglycaemia in patients treated with oral antidiabetic agents or insulin. Glycaemic control should be closely monitored particularly during the first month of treatment with an ACE inhibitor (see section 4.5).

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

Neutropenia/ Agranulocytosis
ACE inhibitors have been rarely associated with neutropenia, agranulocytosis, thrombocytopenia, anaemia and bone marrow depression in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a connective disease with the concomitant use of immunosuppressive therapy, allopurinol, procainamide or other agents which may be associated with neutropenia/agranulocytosis. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) as this could be a sign of neutropenia (see section 4.5).

Agranulocytosis has been rarely reported during treatment with quinapril. As with other ACE inhibitors, monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Surgery/Anaesthesia
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, quinapril may block angiotensin-II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute 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 hydrochlorothiazide 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 sulfonamide or penicillin allergy.

Lithium
Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Tetracycline and other drugs that interact with magnesium
Beacause of the presence of magnesium carbonate in the formulation, quinapril has been shown in healthy volunteers to reduce the absorption of tetracycline in concomitant administration by 28-37%. It is recommended that concomitant administration with tetracycline be avoided. This interaction should be considered if coprescribing quinapril and tetracycline.

Agents increasing serum potassium
Quinapril/hydrochlorothiazide contains a thiazide diuretic, which tends to increase the urinary excretion of potassium but it also contains an ACE inhibitor, which tends to conserve potassium by lowering aldosterone levels. It is not advisable to routinely add potassium sparing diuretics or potassium supplements as this may result in elevated serum potassium.

Other diuretics
Quinapril/hydrochlorothiazide contains a diuretic. Concomitant use of another diuretic may have an additive effect. Also, patients on diuretics, especially those who are volume and/or salt depleted, may experience an excessive reduction of blood pressure on initiation of therapy, or with increased dosage of an ACE inhibitor.

Other antihypertensive drugs
There may be an additive effect or potentiation when quinapril/hydrochlorothiazide is combined with other antihypertensive drugs such as nitrates or vasodilators.

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

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

Surgery/anaesthesia
Although no data are available to indicate there is an interaction between quinapril and anaesthetic agents that produces hypotension, caution should be exercised when patients undergo major surgery or anaesthesia since ACE inhibitors have been shown to block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion (see Section 4.4).

Thiazides may decrease the arterial response to noradrenaline. In emergency surgery pre-anaesthetic and anaesthetic agents should be administered in reduced doses. Thiazides may increase the response to tubocurarine.

Lithium
Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy due to the sodium-losing effect of these agents. With quinapril/hydrochlorothiazide, the risk of lithium toxicity may be increased.
Quinapril/hydrochlorothiazide should be administered with caution and frequent monitoring of serum lithium levels is recommended.

Amphotericin B (parenteral), carbenoxolone, corticosteroids, corticotropin (ACTH) or stimulant laxatives
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

Non-steroidal anti-inflammatory drugs
In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium sparing, and thiazide diuretics and may reduce the antihypertensive effect of ACE inhibitors. Therefore, when quinapril/hydrochlorothiazide and nonsteroidal anti-inflammatory agents are used concomitantly the patients should be observed closely to determine if the desired effect of quinapril/hydrochlorothiazide is obtained. Furthermore, it has been described that 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 and occur especially in patients with compromised renal function. Rarely, acute renal failure may occur, particularly in patients with compromised renal function such as the elderly or dehydrated. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Allopurinol, cytostatic and immunosuppressive agents, systemic corticosteroids or procainamide
Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

Alcohol, barbiturates or narcotics
Potentiation of orthostatic hypotension may occur.

Drugs associated with torsades de pointes
Due to the risk of hypokalaemia, caution should be used when hydrochlorothiazide is co-administered with medicines such as digitalis glycosides or agents associated with torsades de pointes.

Antacids
Antacids may decrease the bioavailability of quinapril/hydrochlorothiazide.

Antidiabetic drugs (oral hypoglycaemic agents and insulin)
In diabetic patients ACE inhibitors may enhance insulin sensitivity and have been associated with hypoglycaemia in patients treated with oral antidiabetic agents or insulin. Glycaemic control should be

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

closely monitored particularly during the first month of treatment with an ACE inhibitor (see section 4.4).

Pressor amines (e.g., norepinephrine)
Possible decreased response to pressor amines, but not sufficient to preclude their use.

Anion exchange resins
Absorption of hydrochlorothiazide is impaired in the presence of anion exchange resins, such as cholestyramine and colestipol. Single doses of the resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 % and 43 %, respectively. The agents should be taken with intervals of several hours.

Other Agents
No clinically important pharmacokinetic interactions occurred when quinapril was used concomitantly with propranolol, hydrochlorothiazide, digoxin or cimetidine.

The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril co-administration twice daily.

Tricyclic antidepressants/Antipsychotics/Anesthetics/Narcotics
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants, narcotics and antipsychotics with ACE inhibitors may result in further reduction of blood pressure. Postural hypotension may occur. (See section 4.4).

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Heparin
An increase in serum potassium concentration is possible.

Calcium salts
Increased serum calcium levels due to decreased excretion may occur when administered concurrently with thiazide diuretics.

Cardiac glycosides
Enhanced risk of digitalis toxicity is associated with thiazide induced hypokalaemia.

Sulphonamide diuretics should be taken at least one hour before or four to six hours after this medicinal product.

Trimethoprim
Trimethoprim (with its amiloride-like action in the distal tubules) used concomitantly with ACE-inhibitors and thiazides may precipitate hyperkalaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

ACE-inhibitors
The use of ACE inhibitors is not recommended during the first trimester of pregnancy (see section 4.4). The use of ACE inhibitors is contraindicated during the second and third trimester of pregnancy (see sections 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.

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

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). (See section 5.3.) Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breastfeeding

Quinapril
Limited pharmacokinetic data demonstrate very low concentrations in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant, the use of Quinapril/Hydrochlorothiazide Actavis 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 Quinapril/Hydrochlorothiazide Actavis 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.

Hydrochlorothiazide
Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Quinapril/Hydrochlorothiazide Actavis during breast feeding is not recommended. If Quinapril/Hydrochlorothiazide Actavis is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

The medicinal product has minor or moderate influence on the ability to drive and use machines. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur, especially when initiating therapy.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with quinapril/hydrochlorothiazide with the following frequencies: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated form the available data).

System Organ Class	Frequency	Undesirable effects
Infections and infestations	Common	Bronchitis, upper respiratory tract infection, pharyngitis[#], rhinitis[#]
	Uncommon	Viral infection, urinary tract infection,

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

		sinusitis
Blood and lymphatic system disorders	Not known	Agranulocytosis[##], haemolytic anemia[#∞], neutropenia[##], thrombocytopenia[#], eosinophilia[#]
Immune system disorders	Not known	Anaphylactoid reaction[#]
Metabolism and nutrition disorders	Common	Hyperkalaemia[##], gout[#], hyperuricaemia[#]
	Uncommon	Glucose tolerance impaired
Psychiatric disorders	Common	Insomnia[#]
	Uncommon	Confusional state[#], depression[#], nervousness[#]
Nervous system disorders	Common	Dizziness[#], headache[#], somnolence[#]
	Uncommon	Transient ischaemic attack[#], syncope[#], paraesthesia[#], dysgeusia[#]
	Rare	Balance disorder
	Not known	Cerebrovascular accident[#]
Eye disorders	Uncommon	Amblyopia[#]
	Very rare	Vision blurred[#]
Ear and labyrinth disorders	Uncommon	Vertigo[#], tinnitus[#]
Cardiac disorders	Common	Angina pectoris[##], tachycardia[#], palpitations[#], myocardial infarction[#]
	Not known	Arrhythmia
Vascular disorders	Common	Vasodilatation[#]
	Uncommon	Hypotension[#]
	Not known	Orthostatic hypotension[#]
Respiratory, thoracic and mediastinal disorders	Common	Cough[#]
	Uncommon	Dyspnoea[#], dry throat
	Rare	Eosinophilic pneumonia[##], upper airways obstruction by angioedema (that may be fatal)[#]
	Not known	Bronchospasm#
Gastrointestinal disorders	Common	Vomiting[#], diarrhoea[#], dyspepsia[#], abdominal pain[#], nausea[#]
	Uncommon	Flatulence[#], dry mouth[#]
	Rare	Constipation, glossitis
	Very Rare	Ileus[#], small bowel angioedema
	Not known	Pancreatitis[#]
Hepatobiliary disorders	Not known	Hepatitis[#], jaundice cholestatic[#]
Skin and subcutaneous tissue disorders	Uncommon	Alopecia[#], photosensitivity reaction[#], pruritus[#], rash[#], angioedema[##], hyperhidrosis[##]
	Rare	Skin disorders may be associated with fever, muscle and joint pain (myalgias, arthralgias, arthritis), vascular inflammation (vasculitis), Dermatitis psoriasisiforms[#]
	Very rare	Urticaria[#]
	Not known	Toxic epidermal necrolysis[#], erythema multiforme[#], dermatitis exfoliative[#], pemphigus[#], purpura, Stevens Johnson syndrome[#]
Musculoskeletal, connective tissue and bone disorders	Common	Back pain[#], myalgia[#]
	Uncommon	Arthralgia[#]

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

	Not known	Systemic lupus erythematosus
Renal and urinary disorders	Uncommon	Renal impairment[#], proteinuria
	Not known	Tubulointerstitial nephritis
Reproductive system and breast disorders	Uncommon	Erectile dysfunction[#]
General disorders and administration site conditions	Common	Fatigue[#], asthenia[#], chest pain[#]
	Uncommon	Generalised oedema[##], pyrexia[#], oedema peripheral[#]
	Not known	Serositis
Investigations	Common	Blood creatinine increased[#], blood urea increased[#]*
	Not known	Blood cholesterol increased[#], blood triglycerides increased[#], haematocrit decreased[#], hepatic enzyme increased, blood bilirubin increased, antinuclear antibody increased[#], red blood cell sedimentation rate increased.

* Such increases are more likely to occur in patients receiving concomitant diuretic therapy than those on monotherapy with quinapril. These observed increases will often reverse on continued therapy.

Adverse reactions associated with quinapril component, frequencies observed when taking quinapril/hydrochlorothiazide.

Adverse reactions associated with quinapril component, frequencies observed in quinapril, adverse reactions not associated with quinapril/hydrochlorothiazide component.

∞ In patients with a congenital G-6-PDH deficiency, individual cases of haemolytic anaemia[#] have been reported.

Clinical Laboratory Test Findings:

Serum Electrolytes: (See section 4.4).

Serum Uric Acid, Glucose, Magnesium, Parathyroid Function tests and Calcium: (See section 4.4).

Haematology test: (See section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

No data are available for quinapril/hydrochlorothiazide with respect to overdosage in humans.
The most likely clinical manifestation would be symptoms attributable to quinapril monotherapy overdosage such as severe hypotension, which would usually be treated by infusion of intravenous normal saline.
The most common signs and symptoms observed for hydrochlorothiazide monotherapy overdosage are those caused by electrolyte depletion (hypokalaemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrythmias.
No specific information is available on the treatment of overdosage with

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

quinapril/hydrochlorothiazide.

Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. Treatment is symptomatic and supportive consistent with established medical care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and diuretics, ATC code: C09BA06
Quinapril/Hydrochlorothiazide Actavis is a fixed combination of the ACE inhibitor, quinapril, and a diuretic, hydrochlorothiazide. Concomitant administration of these agents reduces blood pressure to a greater degree than either component alone, given as monotherapy. Quinapril may, like other ACE inhibitors, counteract the loss of potassium that is inherent with hydrochlorothiazide.

Quinapril is a prodrug, which is hydrolysed to the active metabolite quinaprilat, a potent long-acting inhibitor of angiotensin converting enzyme (ACE) in plasma and tissue. ACE catalyses the conversion of angiotensin-I to angiotensin-II, which is a potent vasoconstrictor. Inhibition of ACE results in decreased concentrations of angiotensin-II and reduced aldosterone secretion. Bradykinin metabolism is probably also inhibited. In clinical studies quinapril has been found to be lipid neutral and has no negative effect on glucose metabolism. Quinapril reduces the total peripheral and renal arterial resistance.
In general there are no clinically relevant changes in renal blood flow or glomerular filtration rate. Quinaprilat results in a reduction of prone, sitting and standing blood pressure. The peak effect is achieved after 2-4 hours at recommended doses. Achievement of maximum blood pressure lowering effect may require 2-4 weeks of therapy in some patients. A decrease in left ventricular hypertrophy was observed with quinapril in experimental models of hypertension in animals. Morbidity/mortality data is lacking.

Hydrochlorothiazide is a thiazide diuretic and an antihypertensive agent that increases renin activity in plasma. Hydrochlorothiazide decreases the renal reabsorption of electrolytes in distal tubuli and increases the excretion of sodium, chloride, potassium, magnesium, bicarbonate and water. The excretion of calcium may be reduced. Concomitant administration of quinapril and hydrochlorothiazide produces a stronger hypotensive effect than that of either of the agents, given alone as monotherapy.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

group than in the placebo group."

5.2 Pharmacokinetic properties

Quinapril
The bioavailability of the active metabolite, quinaprilat, is 30-40 % of the given oral dose of quinapril. Peak plasma concentrations are reached after approximately 2 hours. The absorption of quinapril is not affected by concurrent food intake, but an extremely high fat content in the food may reduce uptake. Approximately 97 % of the drug is bound to plasma proteins. With repeat dosing quinaprilat has a half life of 3 hours. Steady state is reached in 2-3 days. Quinaprilat is mainly excreted unchanged by the kidneys. The clearance is 220 ml/min.

In patients with renal dysfunction the half-life of quinaprilat is prolonged and the plasma quinaprilat concentrations are elevated. In patients with severely impaired hepatic function the concentrations of quinaprilat are reduced due to inhibited hydrolysis of quinapril.

Lactation
After a single oral dose of 20 mg of quinapril in six breast-feeding women, the M/P (milk to plasma ratio) for quinapril was 0.12. Quinapril was not detected in milk after 4 hours after the dose. Quinalaprilat milk levels were undetectable (<5 µg/L) at all time points. It is estimated that a breastfed infant would receive about 1.6 % of the maternal weight-adjusted dosage of quinapril.

Hydrochlorothiazide
The bioavailability is 60-80 %. The diuretic effect is evident within 2 hours of administration, with a maximum effect after ca 4 hours. The effect is maintained for 6-12 hours. Hydrochlorothiazide is excreted unchanged through the kidneys. The mean plasma half-life is in the range of 5-15 hours.

The half-life of Hydrochlorothiazide is prolonged in patients with impaired renal function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. No studies regarding genotoxicity or carcinogenicity of the combination (quinapril/hydrochlorothiazide) have been carried out. Reproductive toxicity studies in rats suggest that quinapril and/or hydrochlorothiazide has no negative effects on fertility and reproductive performance, and is not teratogenic. ACE inhibitors, as a class, have been shown to be foetotoxic (causing injury and/or death to the foetus) when given in the second or third trimester.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium carbonate, heavy
Calcium hydrogen phosphate, anhydrous
Pregelatinised starch (maize)
Croscarmellose sodium
Magnesium stearate

Film coating
Hydroxypropylcellulose
Hypromellose
Titanium dioxide (E171)
Macrogol
Iron oxide, yellow (E 172)

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC

Iron oxide, red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Do not store above 30˚C.
Blisters: Store in the original carton to protect from moisture.
Tablet containers: Keep the container tightly closed.

6.5 Nature and content of container

Blister packs (Aluminium/polyamide/PVC): 10, 14, 30, 50 and 100 tablets
Tablet container (polyethylene): 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

For SE:
Actavis Group PTC ehf.
Reykjavíkurvegur 76-78
220 Hafnarfjörður
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

For SE:
25781, 25782, 25783

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2013-10-16

10. DATE OF REVISION OF THE TEXT

2014-11-17

PDF rendering: Titel 00116818, Version 7.0, Namn Quinapril_Hydrochlorothiazide Actavis film-coated tablet ENG SmPC