Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Quinapril/Hydrochlorothiazide Aurobindo 10mg/12.5mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of quinapril equivalent to 10.83 mg of quinapril hydrochloride and 12.5 mg hydrochlorothiazide. Excipient: Each film-coated tablet contains 18.45 mg of lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablets
Pink colored, scored, oval shaped, biconvex, film-coated tablets debossed with ‘D’ on scored side and ‘18’ on other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Quinapril/Hydrochlorothiazide Aurobindo is indicated as substitution therapy only in adult patients with essential hypertension already adequately controlled with quinapril and hydrochlorothiazide given concurrently.

4.2 Posology and method of administration

Posology
Patients receiving quinapril and hydrochlorothiazide from separate tablets may be switched to a combination tablets of Quinapril/Hydrochlorothiazide Aurobindo containing the same component doses.

Adults:
The recommended dose of Quinapril/Hydrochlorothiazide Aurobindo is one tablet per day.

Renal impairment
Due to hydrochlorothiazide component, Quinapril/Hydrochlorothiazide Aurobindo is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see sections 4.3, 4.4 and 5.2).

Elderly patients (>65 years old)
The dose should be kept as low as possible commensurate with achievement of adequate blood pressure control.

Children and adolescents (less than 18 years of age)
Quinapril/Hydrochlorothiazide Aurobindo is not recommended for use in children and adolescents due to lack of data on safety and efficacy.

Method of administration
For oral use.
To be taken with or without food. The dose should always be taken at about the same time of day to help increase compliance.

4.3 Contraindications

- Quinapril/HCTZ is contraindicated in women who are pregnant, intend to become pregnant, or of childbearing potential who are not using adequate contraceptive measures (see Sections 4.4 and 4.6).
- Quinapril/HCTZ is contraindicated in patients with hypersensitivity to any of the ingredients including patients with a history of angioedema related to previous treatment with ACE inhibitors.
- Quinapril/HCTZ is contraindicated in patients with hereditary/idiopathic angioneurotic oedema.
- Quinapril/HCTZ should not be used in patients with ventricular outflow obstruction.
- Quinapril/HCTZ is contraindicated in patients with anuria or with severe renal dysfunction.
- Quinapril/HCTZ is contraindicated in patients with hypersensitivity to other sulphonamide-derived drugs.

4.4 Special warnings and precautions for use

Quinapril/HCTZ should be used with caution in selected patients with aortic stenosis.

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/HCTZ 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).

Quinapril/HCTZ should be used cautiously in patients receiving concomitant therapy with other antihypertensive agents. The thiazide component of quinapril/HCTZ 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; 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. Quinapril/HCTZ 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.

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 rennin-angiotensin- aldosterone system, treatment with 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.

Renal Disease:
Quinapril/HCTZ 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 10-20ml/min) thiazides are generally ineffective in such patients, and the effects of repeated dosing may be cumulative.

There is insufficient experience in patients with severe renal impairment (creatinine clearance <10 ml/min).

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.

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. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

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

Impaired Hepatic Function:
Quinapril/HCTZ should be used with caution in patients with impaired hepatic function 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). Patients who during ACE inhibitor therapy experience jaundice or clearly elevated hepatic enzymes should discontinue quinapril/HCTZ and receive appropriate medical follow-up.

Immune-mediated drug reactions/ Anaphylactoid reactions:
Desensitisation: Patients receiving ACE inhibitors during desensitizing 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 rechallenge.

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.

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:
Patients receiving quinapril/HCTZ 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.

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:
Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (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 (see Section 4.5).

Neutropenia/Agranulocytosis:
ACE inhibitors have been rarely associated with agranulocytosis 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 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.

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:
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose/galactose malabsorption should not use this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Tetracycline and other drugs that interact with magnesium:
Because 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/HCTZ 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/HCTZ 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/HCTZ is combined with other antihypertensive drugs such as nitrates or vasodilators.

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/HCTZ, the risk of lithium toxicity may be increased.
Quinapril/HCTZ should be administered with caution and frequent monitoring of serum lithium levels is

recommended.

Corticosteroids, ACTH:
Intensified electrolyte depletion, particularly hypokalaemia has been observed.

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/HCTZ and nonsteroidal anti-inflammatory agents are used concomitantly the patients should be observed closely to determine if the desired effect of quinapril/HCTZ 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.

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 potential risk of hypokalemia, 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/HCTZ .

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 closely monitored (see Section 4.4).

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.

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.

Lactation:
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 Aurobindo 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 Aurobindo 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 Aurobindo during breast feeding is not recommended. If Quinapril/Hydrochlorothiazide Aurobindo is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

The ability to engage in activities such as operating machinery or operating a motor vehicle may be impaired.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with quinapril/HCTZ 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
Blood and the lymphatic system disorders	Not known	Agranulocytosis##, haemolytic anemia#, neutropenia##, thrombocytopenia#
Immune system disorders	Not known	Anaphylactoid reaction#
Metabolism and nutrition disorders	Common	Hyperkalaemia##
Psychiatric disorders	Common	Insomnia#
	Uncommon	Confusion#, depression#, nervousness#
Nervous system disorders	Common	Dizziness#, headache#, somnolence#
	Uncommon	Paraesthesia#, Transient ischaemic attacks#
	Rare	Balance disorder
	Not known	Cerebral haemorrhage#
Eye disorders	Uncommon	Amblyopia#
	Very Rare	Blurred vision#
Ear and labyrinth disorders	Uncommon	Tinnitus#, vertigo#

Cardiac disorders	Common	Myocardial infarction#
	Uncommon	Angina pectoris##, tachycardia#, palpitations#
	Not known	Arrhythmia
Vascular disorders	Common	Vasodilation#
	Uncommon	Hypotension#, syncope#
	Not known	Postural hypotension#
Respiratory, thoracic and mediastinal disorders	Common	Bronchitis, cough#, pharyngitis#, rhinitis#, upper respiratory tract infection
	Uncommon	Dyspnoea#, sinusitis
	Rare	Eosiniphilic pneumonitis##, angioneurotic oedema#
	Not known	Bronchospasm#
Gastrointestinal disorders	Common	Abdominal pain#, diarrhoea#, dyspepsia#, nausea#, vomiting#
	Uncommon	Flatulence#, dry mouth or throat#, altered taste#
	Rare	Constipation, glossitis
	Very Rare	Ileus#, intestinal angioedema
	Not known	Pancreatitis#
Hepato-biliary disorders	Not known	Hepatitis#, cholestatic icterus#
Skin and subcutaneous tissue disorders	Uncommon	Alopecia#, photosensitivity# pruritus#, rash#, angioedema##, increased perspiration##
	Rare	Skin changes may be associated with fever, muscle and joint pain (myalgias, arthralgias, arthritis), vascular inflammation (vasculitis), psoriasis-like efflorescence#
	Very Rare	Urticaria#
	Not known	Toxic epidermal necrolysis#, erythema multiforme#, exfoliative dermatitis#, pemphigus#, purpura, Stevens-Johnson syndrome#, inflammations of serous tissues and certain changes in laboratory values (eosinophilia# and/or elevated ANA titers#, elevated ESR)
Musculoskeletal, connective tissue and bone disorders	Common	Back pain#, myalgia#, hyperuricaemia#, gout#
	Uncommon	Arthralgia#
Renal and urinary disorders	Uncommon	Renal dysfunction#, proteinuria, urinary tract infection
	Not known	Interstitial nephritis
Reproductive system and breast disorders	Uncommon	Impotence#
General disorders and administration site conditions	Common	Asthenia#, Chest pain#, fatigue#
	Uncommon	Fever#, generalised oedema#,#, peripheral oedema#
Investigations	Common	Increased serum creatinine#,

		increased blood urea nitrogen#*
	Not known	Increases in cholesterol# and triglyceride levels#. Decreases in hematocrit# and WCC# as well as elevation in liver enzymes and serum bilirubin. In patients with a congenital G-6-PDH deficiency, individual cases of haemolytic anaemia# have been reported
Infections and infestations	Uncommon	Viral infection
Endocrine disorders	Uncommon	Insulin requirements in diabetic patients may be altered by thiazides and latent diabetes mellitus may occur#

* 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/HCTZ.

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

Clinical Laboratory Test Findings:
Serum Electrolytes: (See section 4.4).
Serum Uric Acid, Glucose, Magnesium, PBI, Parathyroid Function tests and Calcium: (See section 4.4).
Haematology test: (See section 4.4).

4.9 Overdose

No data are available for quinapril/HCTZ 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 HCTZ 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 quinapril/HCTZ.

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: Quinapril and diuretics, ATC code: C09BA06

Quinapril/Hydrochlorothiazide Aurobindo 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 longacting 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 filtrationrate. 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.

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 active substance 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.

After a single oral dose of 20 mg of quinapril in six breast-feeding women, Milk/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

Preclinical data reveal no special hazard for humans based on conventional studies of 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 fetotoxic (causing injury and/or death to the fetus) when given in the second or third trimester.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Magnesium carbonate heavy
Crospovidone (Type A)
Povidone (K30)
Magnesium stearate

Tablet coat: (Opadry pink)
Hypromellose
Titanium dioxide (E171)
Hydroxypropyl cellulose
Macrogol 400
Iron oxide red (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Blister packs Polyamide/Al/PV/Al blister: 7, 10, 14, 20, 28, 30, 42, 50, 56, 60, 84, 90, 98, 100, 156, 250 and 500 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Limited UK
Ares, Odyssey Business Park
West End Road
South Ruislip
HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1311/9/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 October 2010

10 DATE OF REVISION OF THE TEXT

June 2012