1. NAME OF THE MEDICINAL PRODUCT

Quinapril 5 mg Film coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg quinapril (as hydrochloride).

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated Tablet
Red-brown, oval, biconvex tablet, scored on both sides and marked I.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
For the treatment of all grades of essential hypertension. Quinapril film coated tablets is effective as monotherapy or concomitantly with diuretics in patients with hypertension.

Congestive Heart Failure
For the treatment of congestive heart failure when given concomitantly with a diuretic and/or cardiac glycoside. Treatment of congestive heart failure with Quinapril film coated tablets should always be initiated under close medical supervision.

4.2 Posology and method of administration

For oral use.

Adults

Hypertension
Monotherapy: The recommended initial dosage is 10 mg once daily in uncomplicated hypertension. Depending upon clinical response, patient's dosage may be titrated (by doubling the dose allowing adequate time for dosage adjustment) to a maintenance dosage of 20 to 40 mg/day given as a single dose or divided into 2 doses. Long-term control is maintained in most patients with a single daily dosage regimen. Patients have been treated with dosages up to and including 80 mg/day.
Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of 2.5 mg of Quinapril film coated tablets is recommended in patients who are being treated with a diuretic. After this the dosage of Quinapril film coated tablets should be titrated (as described above) to the optimal response.

Congestive Heart Failure

In order to closely monitor patients for symptomatic hypotension, a single 2.5 mg initial dosage is recommended. After this, patients should be titrated to an effective dose: (up to 40 mg/day) given in 1 or 2 doses with concomitant diuretic and/or cardiac glycoside therapy. Patients are often maintained effectively on doses of 10-20 mg/day given with concomitant therapy.

Severe Heart Failure

In the treatment of severe or unstable congestive heart failure, Quinapril film coated tablets should always be initiated in hospital under close medical supervision.

Other patients who may also be considered to be at higher risk and should have treatment initiated in hospital include: patients who are on high dose loop diuretics (e.g.> 80 mg frusemide) or on multiple diuretic therapy, have hypovolaemia, hyponatraemia (serum sodium < 130 mgEq/l) or systolic blood pressure < 90 mm Hg, are on high dose vasodilator therapy, have a serum creatinine> 150 µmol/l or are aged 70 years or over.

Elderly/Renal Impairment

In elderly patients and in patients with a creatinine clearance of less than 40 ml/min, an initial dosage in essential hypertension of 2.5 mg is recommended followed by titration to the optimal response.

Children

(6 - 12 years)

Not recommended. Safety and efficacy in children have not been established.

4.3 Contraindications

Quinapril Film Coated Tablets are contraindicated in the following circumstances:

- -In patients with hypersensitivity to any of the ingredients.
- -Throughout pregnancy (see section 4.6)
- -In nursing mothers (see section 4.6)
- -In patients with a history of angioedema related to previous treatment with ACE inhibitors.
- -In patients with hereditary/idiopathic angioneurotic oedema.

4.4 Special warnings and precautions for use

Quinapril film coated tablets should not be used in patients with aortic stenosis or outflow obstruction.

Patients haemodialysed using high-flux polyacrylonitrile ('AN69') membranes are very likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. It is best therefore, that this combination 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. Therefore, this method should not be used in patients treated with ACE inhibitors.

Anaphylactoid reactions: Patients receiving ACE inhibitors during desensitising treatment with hymenoptera venom have experienced life threatening anaphylactoid reactions. These

reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each desensitisation.

In patients with renal insufficiency, monitoring of renal function during therapy should be performed as deemed appropriate; although in the majority renal function will not alter or may improve.

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

The half-life of quinaprilat is prolonged as creatinine clearance falls. Patients with a creatinine clearance of <40 ml/min require a lower initial dosage of quinapril. 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 short-lived, 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.

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. Black patients receiving ACE inhibitor therapy generally have a higher incidence of angioedema than non-black patients and a lesser reduction in blood pressure.

Hypotension: Symptomatic hypotension was rarely seen in hypertensive patients treated with Quinapril film coated tablets, but it is a possible consequence of ACE inhibition therapy particularly in salt/volume depleted patients such as those previously treated with diuretics, who have a dietary salt reduction, or who are on dialysis. 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 any concomitant diuretic therapy should be considered if this event occurs.

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 collagen vascular disease. As with other ACE inhibitors, monitoring of white blood cell counts in patients with collagen vascular disease and/or renal diseases should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Tetracycline: Because of the presence of magnesium carbonate in the formulation, Quinapril film coated tablets 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.

Concomitant diuretic therapy: Patients treated with diuretics may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Quinapril film coated tablets. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake before the initial dose of Quinapril. If discontinuation of the diuretic is not possible, medical supervision should be provided for up to two hours following administration of the initial dose.

Agents increasing serum potassium: Concomitant treatments with potassium sparing diuretics, potassium supplements or potassium salts should be used with caution and with appropriate monitoring of serum potassium. As with other ACE inhibitors, patients using quinapril alone may have elevated serum potassium levels. When administered concomitantly, quinapril may reduce the hypokalaemia induced by thiazide diuretics.

Surgery/anaesthesia: Although no data are available to indicate there is an interaction between Quinapril film coated tablets and anaesthetic agents that produces hypotension, in patients who are to undergo major surgery or anaesthesia caution should be exercised since angiotensin converting enzyme 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.

Lithium**:** 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. These drugs should be co-administered with care and frequent monitoring of serum lithium levels is recommended. If a diuretic is also employed, it may increase the risk of lithium toxicity.

Non-steroidal anti-inflammatory drugs (NSAIDs): In some patients, the administration of a non-steroidal anti-inflammatory agent may reduce the antihypertensive effect of ACE inhibitors. 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.

Other antihypertensive drugs: There may be an additive effect of potentiation.

Antacids: May decrease the bioavailability of Quinapril film coated tablets.

Antidiabetic drugs (oral hypoglycaemic agents and insulin): Dosage adjustments of the antidiabetic drug may be required.

4.6 Pregnancy and lactation

Pregnancy

Quinapril film coated tablets are contraindicated throughout pregnancy.

Quinapril film coated tablets have been shown to be foetotoxic in rabbits. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, most probably representing decreased renal function in the foetus, limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios. If a woman becomes pregnant while receiving Quinapril film coated tablets, then the drug should be discontinued as soon as possible. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If oliguria occurs, attention should be directed towards support of blood pressure and renal perfusion.

Lactation

Quinapril film coated tablets should not be used in nursing mothers.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The most frequent clinical adverse reactions in hypertension and congestive heart failure are headache, dizziness, rhinitis, coughing, upper respiratory tract infection, fatigue, and nausea and vomiting. Other less frequent side effects are dyspepsia, myalgia, chest pain, abdominal pain, diarrhoea, back pain, sinusitis, insomnia, paraesthesia, nervousness, asthenia, pharyngitis, hypotension, palpitations, flatulence, depression, pruritus, rash, impotence, oedema, arthralgia, amblyopia.

Renal dysfunction, angioedema, hypotension, hyperkalaemia, neutropenia, agranulocytosis - see warnings and precautions.

The following side effects have been observed associated with ACE inhibitor therapy:

Cardiovascular: Tachycardia, syncope, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage.

Respiratory: Dyspnoea, glossitis, bronchitis and bronchospasm. In individual cases angioneurotic oedema involving the upper airways has caused fatal airway obstruction.

Gastro-intestinal: Constipation, dry mouth, cholestatic icterus, hepatitis and ileus. Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

Skin, vessels: Urticaria, erythema multiforme, Stevens Johnson syndrome, epidermic necrolysis, psoriasis-like efflorescences, alopecia. May be accompanied by fever, eosinophilia and/or increased ANA-titers.

Nervous: Rarely disorders of balance, confusion, tinnitus, blurred vision and taste disturbances.

Drug/Laboratory: Increases in blood urea and plasma creatinine may occur. Decreases in haematocrit, platelets and white cell count as well as elevation of liver enzymes and serum bilirubin. In patients with a congenital deficiency concerning G-6-PDH individual cases of haemolytic anaemia have been reported.

4.9 Overdose

No data are available with respect to overdosage in humans. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion.

Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

Treatment is symptomatic and supportive consistent with established level of care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C09A A06
Group: Agents acting on the Renin-Angiotensin System / Ace inhibitors, Plain

Quinapril is rapidly de-esterified to quinaprilat (quinapril diacid, the principal metabolite) which is a potent angiotensin-converting enzyme (ACE) inhibitor.

Ace is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the vasoconstrictor angiotensin II which is involved in vascular control and function through many different mechanisms, including stimulation of aldosterone secretion by the adrenal cortex. The mode of action of quinapril in humans and animals is to inhibit circulating and tissue ACE activity, thereby decreasing vasopressor activity and aldosterone secretion.

In animal studies, the antihypertensive effect of quinapril outlasts its inhibitory effect on circulating ACE, whereas, tissue ACE inhibition more closely correlates with the duration of antihypertensive effects. Administration of 10-40 mg of quinapril to patients with mild to severe hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate. Antihypertensive activity commences within one hour with peak effects usually achieved by two to four hours after dosing. Achievement of maximum blood pressure lowering effects may require two weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained in most patients throughout the 24 hour dosing interval and continue during long term therapy.

5.2 Pharmacokinetic properties

Peak plasma Quinapril concentrations are observed within 1 hour of oral administration. The extent of absorption is approximately 60%, and is not influenced by food. Following absorption, Quinapril is de-esterified to its major active metabolite, quinaprilat, and to minor inactive metabolites. Quinapril has an apparent half-life of approximately one hour. Peak plasma quinaprilat concentrations occur approximately 2 hours following an oral dose of quinapril. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of 3 hours. In patients with renal insufficiency and creatinine clearance of $\leq$40ml/min, peak and trough quinaprilat concentrations increase, time to peak concentration increases, apparent half-life increases, and time to steady state may be delayed. The elimination of quinaprilat in the elderly patients >65 years) is also reduced and correlates well with the impaired renal function which frequently occurs in the elderly. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of Quinapril. Studies in rats indicate that Quinapril and its metabolites do not cross the blood-brain barrier.

5.3 Preclinical safety data

The results of the preclinical tests do not add anything of further significance to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

TABLET CORE:
Magnesium carbonate
Calcium hydrogen phosphate
Magnesium stearate
Starch pregelatinised
Croscarmellose sodium

COATING:
Opadry Red
-Hypromellose
-Hydroxypropyl cellulose
-Macrogol

-Red iron oxide (E172)
-Titanium dioxide (E171)

6.2. Incompatibilities.

Not applicable.

6.3. Shelf life

18 months

6.4. Special precautions for storage

Do not store above 25°C
Store in the original packaging.

6.5. Nature and contents of container

(Al/Al) blister strip
Quinapril 5 mg film coated tablets are supplied in blister packs of 7 and 10 tablets.

6.6. Instruction for use and handling

No special instructions needed.

7. MARKETING AUTHORISATION HOLDER

Winthrop Pharmaceuticals UK Limited
One Onslow Street
Guildford
Surrey
GU1 4YS
UK

8. MARKETING AUTHORISATION NUMBER

PL 17780/0223

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9th June 2005

10. DATE OF REVISION OF THE TEXT