IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0966/012/003
Case No: 2059773

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Ergha Healthcare Ltd

Damastown, **Mulhuddart**, **Dublin 15**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Quinapro 20 mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **25/06/2009** until **03/11/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Quinapro 20 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Quinapril hydrochloride 21.664 mg
(Equivalent to 20 mg quinapril base)

3 PHARMACEUTICAL FORM

White, oval film-coated tablets debossed “20” on one side and scoreline on the other.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. For the treatment of all grades of essential hypertension. Quinapro is effective as monotherapy or concomitantly with diuretics in patients with hypertension.

2. For the treatment of congestive heart failure when given concomitantly with a diuretic and/or cardiac glycoside. Treatment of congestive heart failure with Quinapro 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. 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 80 mg/day.

Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of 5 mg of Quinapro is recommended in patients who are also being treated with a diuretic. After this, the dosage of Quinapro should be titrated (by doubling the dose allowing adequate time for dosage adjustment) to the optimal response.

Congestive Heart Failure:
In order to closely monitor patients for symptomatic hypotension, a single 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 usually maintained effectively on doses of 10-20 mg/day given with concomitant therapy.

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

Elderly:
Age alone does not appear to affect the efficacy or safety profile of quinapril. Therefore, the recommended initial dosage in hypertension of quinapril in elderly patients is 10mg given once daily followed by titration to the optimal response.

Children:
(6 - 12 years)

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

Patients with renal insufficiency:
In patients with a creatinine clearance of less than 60 ml/min, an initial dosage in essential hypertension of 5 mg once daily is recommended followed by titration to the optimal response. Kinetic data indicate that the apparent elimination half-life of quinaprilat increases as creatinine clearance decreases.

4.3 Contraindications

Hypersensitivity to any of the ingredients.

Second and third trimesters of pregnancy (see sections 4.4 and 4.6). Quinapro has 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, presumably 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. Should a woman become pregnant while receiving ACE inhibitors, 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 toward support of blood pressure and renal perfusion.

Use in patients with subaortic stenosis.

Use in patients with a history of angioneurotic oedema relating to previous treatment with an ACE inhibitor.

4.4 Special warnings and precautions for use

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.

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.

The half-life of quinaprilat is prolonged as creatinine clearance falls. Patients with a creatinine clearance of <60ml/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 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, when combined with a diuretic should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. The metabolism of quinalapril to quinaprilat is normally dependent upon hepatic esterase. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired desterification of quinapril.

Angioneurotic oedema
Angioneurotic oedema has been reported rarely with ACE inhibitors including Quinapro. In some cases symptoms have been observed up to 2 years after initiation of treatment. Such reactions should be regarded as an indication to discontinue therapy immediately and the patient closely monitored. Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms. These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue glottis or larynx, likely to cause airways obstruction, appropriate therapy such as subcutaneous adrenaline (0.5 ml 1:1000) should be administered promptly when indicated.

Caution should be exercised in those known to be hypersensitive to other ACE inhibitors, and particularly those with obstructive airways disease. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see also section 4.3, Contraindications).

Black patients receiving ACE inhibitor therapy have been shown to have a higher incidence of angioedema compared to non-black patients.

Intestinal angioedema
Intestinal angioedema has been reported in patients treated with ACE inhibitor. 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, 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.

Other hypersensitivity reactions have been reported.

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.

Hypotension: Symptomatic hypotension was rarely seen in hypertensive patients treated with Quinapro 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. Any electrolyte or fluid inadequacy should be corrected preferably before initial dose of the product. Careful medical supervision is necessary for a period after dosing.

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.

Hypoglycaemia: ACE inhibitors may enhance insulin sensitivity and have been associated with hypoglycaemia in diabetic patients on insulin or oral hypoglycaemic agents; closer monitoring of diabetic patients may be required, especially in the first few weeks of treatment.

LDL apheresis: Patients undergoing low-density lipoprotein apheresis with dextran-sulphate absorption when treated concomitantly with ACE inhibitor have reported anaphylactoid reactions.

Patients with rare hereditary problems with galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

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

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 treatment should be started (see sections 4.3 and 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Tetracycline: Because of the presence of magnesium carbonate in the formulation Quinapro 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 Quinapro. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Quinapro. If discontinuation of the diuretic is not possible, medical supervision should be provided for up to two hours following administration of the initial dose.

Other anti-hypertensive agents: ß-blockers, methyldopa and diuretics may enhance the hypotensive effects of quinapril, and should only be used under careful supervision. Concomitant propranolol did not affect the pharmacokinetics of quinapril in a single dose study.

Calcium antagonists: There is no experience of concomitant use with Quinapro.

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 caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Agents increasing serum potassium: Concomitant treatments with potassium sparing diuretics, potassium supplements or potassium salts should only be used with caution and with appropriate monitoring of serum potassium, especially in patients with impaired renal function, since by decreasing aldosterone production, Quinapro often causes an increase in serum potassium.

Surgery/anaesthesia: Although no data are available to indicate there is an interaction between Quinapro and anaesthetic agents that produces hypotension, caution should be exercised when patients undergo major surgery or anaesthesia 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.

Concomitant administration of ACE inhibitors and anti-diabetic medicines (insulin, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with the risk of hypoglycaemia. This phenomenon may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Atorvastatin: Co-administration of multiple 10mg doses of atorvastatin with 80mg quinapril resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

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, systematic corticosteroids of procainamide: Concomitant administration with ACE inhibitor may lead to an increased risk of leucopenia.

Antacids: May decrease the bioavailability of quinapril.

Drug interaction studies of quinapril showed: The anticoagulant effect of a single dose of warfarin (measured by the prothrombin time) was not significantly changed by quinapril coadministration twice daily.

Quinapril did not affect the pharmacokinetics of digoxin.

4.6 Pregnancy and lactation

Pregnancy:

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

Lactation:

Limited pharmacokinetic data demonstrated very low concentrations in breast milk (see section 5.2). Although these concentrations seems to be clinically irrelevant, the use of Quinapro 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 Quinapro in breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The most frequent clinical adverse reactions in hypertension and congestive heart failure are headache, dizziness, rhinitis, cough, 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.

Increases (> 1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 3 and 4% respectively of the patients on monotherapy.

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

Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

Renal dysfunction, hypotension, hyperkalaemia, neutropenia, agranulocytosis, angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely. (See also section 4.4, Special warnings and precautions for use).

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

Cardiovascular: postural hypotension, syncope, angina pectoris, tachycardia, palpitations and vasodilation.

Gastrointestinal: abdominal pain, dyspepsia, dry mouth or throat, diarrhoea and flatulence.

Respiratory: dyspnoea and eosinophilic pneumonitis.

Haemic and lymphatic: thrombocytopenia.

Nervous/psychiatric: depression, nervousness, somnolence, vertigo and insomnia.

Integumentary: alopecia, exfoliative dermatitis, increased perspiration, pemphighus, pruritus and rash.

Other: amblyopia, arthralgia, paraesthesia, oedema (peripheral and generalised). Hepatitis, back pain, sinusitis and pharyngitis.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Quinapro is rapidly deesterified to quinaprilat (quinapril diacid, the principal metabolite) which, in human and animal studies, is a potent angiotensin-converting enzyme inhibitor (ACE).

The primary mode of action of Quinapro in humans and animals is to inhibit ACE, thereby decreasing vasopressor activity and aldosterone secretion. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. Quinapro has antihypertensive activity in the presence of low to normal plasma renin concentrations.

Other possible mechanisms contributing to the activity of ACE inhibitors include bradykinin-induced vasodilation, release of prostaglandins, attenuation of sympathetic nervous system activity, and inhibition of tissue enzyme-converting activity.

5.2 Pharmacokinetic properties

Peak plasma Quinapro concentrations are observed within 1 hour of oral administration. The extent of absorption is approximately 60%, and is not influenced by food. Following absorption, Quinapro is deesterified to its major active metabolite, quinaprilat, and to minor inactive metabolites.

Quinapro has an apparent half-life of approximately one hour. Peak plasma quinaprilat concentrations are observed 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 ≤40 ml/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 is also reduced in elderly patients (>65 years) 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 deesterification of Quinapro. Studies in rats indicate that Quinapro and its metabolites do not cross the blood-brain barrier.

Lactation:
After a single oral dose of 20mg 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. Quinaprilat 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 material weight-adjusted dosage of quinapril.

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

Magnesium carbonate, heavy
Calcium hydrogen phosphate, anhydrous
Gelatin
Crospovidone
Magnesium stearate
Opadry II White 03G28692
Hypromellose 6cP
Titanium dioxide (E171)
Macrogol 6000
Macrogol 400

6.2 Incompatibilities

None known.

6.3 Shelf Life

2 years when stored in the original packaging.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blisters in cardboard boxes containing: 2, 7, 14, 28, 28 (calendar), 30, 50, 50 (hospital pack), 56, 100 or 300 (hospital pack: 10 x 30) film-coated tablets.
Not all pack sizes maybe marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ergha Healthcare Ltd
Damastown
Mulhuddart
Dublin 15

8 MARKETING AUTHORISATION NUMBER

PA0966/012/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 November 2005

10 DATE OF REVISION OF THE TEXT

June 2009