

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Accupro 5 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Quinapril hydrochloride 5.416 mg (Equivalent to 5mg quinapril base).
Contains Lactose

For excipients, see Section, 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablets

Product Imported from Greece

Brown, elliptical film-coated tablet with a breakline and imprinted with the dosage strength '5' on both sides

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. For the treatment of all grades of essential hypertension. Accupro 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 Accupro 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 Accupro is recommended in patients who are also being treated with a diuretic. After this the dosage of Accupro should be titrated (by doubling the dose allowing adequate time for dosage adjustment) to the optimal response (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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, Accupro 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 (see section 4.4 Special warnings and precautions for use).

4.3 Contraindications

Hypersensitivity to any of the ingredients

Use in patients with subaortic stenosis.

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

Second and third trimesters of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

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).

Impaired Renal Function: 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 <60 ml/min require a lower initial dosage of quinapril (see section 4.2 Posology and method of administration). 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 quinapril to quinaprilat is normally dependent upon hepatic esterase. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril.

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 rechallenge.

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

Haemodialysis: 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.

Angioneurotic oedema: Angioneurotic oedema has been reported rarely with ACE inhibitors including Accupro. 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.

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 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

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).

Other hypersensitivity reactions have been reported.

Hypotension: Symptomatic hypotension was rarely seen in hypertensive patients treated with Accupro 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.

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 the differential diagnosis of cough.

Patients with rare hereditary problems with galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take 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 Accupro has been shown in healthy volunteers to reduce the absorption of tetracycline in concomitant administration by 28-37%. It is recommended that concomitant administration of tetracycline be avoided.

Concomitant diuretic therapy: Patients treated with diuretics may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Accupro. This hypotensive effect may be effectively minimized by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Accupro. If discontinuation of the diuretic is not possible, medical supervision should be provided for up to two hours following administration of the initial dose (see Section 4.4 Special warnings and precautions for use and Section 4.2 Posology and method of administration).

Other anti-hypertensive agents: beta-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 Accupro.

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

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: Quinapril is an angiotensin-converting enzyme inhibitor capable of lowering aldosterone levels, which in turn can result in a mild elevation in 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, Accupro often causes an increase in serum potassium.

Surgery/anaesthesia: Although no data are available to indicate there is an interaction between Accupro 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.

Antidiabetic drugs: 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.

4.6 Fertility, 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 2nd and 3rd 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). 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).

Accupro has been shown to be foetotoxic in the rabbit. 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. 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.

Lactation:

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 Accupro 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 Accupro in a breast-feeding mother may be considered if this treatment is necessary for the mother and the child is observed for any adverse effect.

4.7 Effects on ability to drive and use machines

The ability to engage in activities such as operating machinery or operating a motor vehicle may be impaired especially when initiating quinapril therapy.

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.

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 Accupro. 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 section 4.4 Special warnings and precautions for use).

The following side effects have been observed associated with ACE inhibitor therapy: The adverse reactions are classified according to frequencies determined from clinical trials data.

Very common $\geq 1/10$ ($\geq 10\%$)

Common $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)

Uncommon $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$)

Rare $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)

Very rare $< 1/10,000$ ($< 0.1\%$)

* If a listed adverse reaction term was not reported in clinical trials it was assumed to be rare, based on reporting rates versus estimated product use worldwide.

Infections and Infestations:

Common: Pharyngitis

Uncommon: Urinary tract infection, Sinusitis

Blood and Lymphatic System Disorders:

Rare: Neutropenia, agranulocytosis, Haemolytic anaemia*, Thrombocytopenia*

Immune System Disorders:

Rare: Anaphylactoid reaction*

Psychiatric Disorders:

Common: Insomnia

Uncommon: Nervousness, Depression

Metabolism and Nutrition Disorders:

Common: Hyperkalaemia

Nervous System Disorders:

Common: Paraesthesia

Uncommon: Somnolence, Vertigo

Eye Disorders:

Uncommon: Amblyopia

Cardiac Disorders:

Uncommon: Angina pectoris, Palpitations, Tachycardia

Vascular Disorders:

Uncommon: Vasodilatation
Rare: Postural hypotension*, Syncope*

Respiratory, Thoracic and Mediastinal Disorders:

Common: Dyspnoea
Rare: Eosinophilic pneumonitis

Gastrointestinal Disorders:

Common: Abdominal pains
Uncommon: Dry mouth or throat, Flatulence, Pancreatitis*

Hepatobiliary Disorders:

Rare: Hepatitis

Skin and Subcutaneous Tissue Disorders:

Uncommon: Pruritus, rash, Increased perspiration
Rare: Alopecia*, Exfoliative dermatitis*, Pemphigus*, Photosensitivity reaction*

Musculoskeletal and Connective Tissue Disorders:

Common: Back pain, myalgia
Uncommon: Arthralgia

Reproductive system and breast disorders:

Uncommon: Impotence

General disorders and administration site conditions:

Common: Asthenia
Uncommon: Edema (peripheral and generalized)

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

ATC Code – CO9AA06, ACE inhibitors, plain.

Accupro is rapidly deesterified to quinaprilat (quinapril diacid, the principal metabolite) which, in human and animal studies, is a potent angiotensin-converting enzyme (ACE) inhibitor. The primary mode of action of Accupro 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. Accupro 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 enzymeconverting activity.

Administration of 10-40 mg of quinapril to patients with mild to moderate 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 Accupro concentrations are observed within 1 hour of oral administration. The extent of absorption is approximately 60%, and is not influenced by food. Following absorption, Accupro is deesterified to its major active metabolite, quinaprilat, and to minor inactive metabolites. Accupro 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 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 is also reduced in elderly patients (>65 years) and correlates well with the impaired renal function which frequently occurs in the elderly. Studies in rats indicate that Accupro and its metabolites do not cross the blood-brain barrier.

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. 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 maternal 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

Heavy magnesium carbonate
Lactose monohydrate
Gelatin
Croscopovidone
Magnesium stearate
Candelilla
Opadry Brown Y-5-9020 G containing:
Hypromellose
Hyprolose
Titanium dioxide (E 171)
Macrogol 400
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister packs of 28 tablets contained in an overlabelled outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

G & A Licensing
Ballymurray
Co. Roscommon
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1447/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation : 25th July 2008

10 DATE OF REVISION OF THE TEXT

August 2010