Quinapril 5mg, 10mg, 20mg and 40mg Tablets

PL 20092/0030-33

UKPAR

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PL 20092/0030-33

LAY SUMMARY

On 21st September 2009, the MHRA granted Lupin (UK) Limited Marketing Authorisations (licences) for Quinapril 5mg, 10mg, 20mg and 40mg Tablets (PL 20092/0030-33).

This medicine contains quinapril hydrochloride, which belongs to a group of medicines called angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors work by widening the blood vessels in the body, which can reduce the pressure in the vessels.

Quinapril is an ACE inhibitor used to treat high blood pressure (hypertension) and to help treat heart failure. Quinapril is effective alone or together with water tablets (diuretics) in patients with hypertension. Quinapril can also be used for the treatment of heart failure when given together with a diuretic and/or cardiac glycoside such as digoxin.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Quinapril 5mg, 10mg, 20mg and 40mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
Quinapril 5mg, 10mg, 20mg and 40mg Tablets

PL 20092/0030-33

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Lupin (UK) Limited Marketing Authorisations for the medicinal products Quinapril 5mg, 10mg, 20mg and 40mg Tablets (PL 20092/0030-33) on 21st September 2009. These products are prescription only medicines (POM) indicated for the treatment of the following indications:

- All grades of essential hypertension. Quinapril Tablet is effective as monotherapy or concomitantly with diuretics in patients with hypertension.

- Congestive heart failure when given concomitantly with a diuretic and/or cardiac glycoside. Treatment of congestive heart failure with Quinapril Tablets should always be initiated under close medical supervision.

These applications for Quinapril 5mg, 10mg, 20mg and 40mg Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal products to Accupro Tablets 5mg (PL 00018/0148), first authorised in the UK to Parke Davis and Company Limited in June 1989, which underwent a change of ownership in October 1997 to Warner Lambert (UK) Limited (PL 00019/0123). This underwent a further change of ownership to Pfizer Limited (PL 00057/0514) in August 2003.

Following oral administration, quinapril is rapidly absorbed and is hydrolysed to the active diacid metabolite, quinaprilat and other inactive metabolites. Mean peak concentrations of quinapril and its active metabolite are reached in 1 hour and 2 hours, respectively. The presence of food in the GIT does not affect $C_{\text{max}}$ but may increase $T_{\text{max}}$. 
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Quinapril hydrochloride

INN: Quinapril hydrochloride
Chemical name: (i) (S)-2-[(S)-N-[(S)-1-carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1-ethyl ester, monohydrochloride

(ii) 3-isoquinolinecarboxylic acid, 2-[2-[[1-ethoxycarbonyl]-3-3phenylpropyl]amino]-1]oxopropyl]-1,2,3,4-tetrahydro-monohydrochloride, [3S-[2[R*)R*)]3R*]]

Structure:

![Structure of Quinapril Hydrochloride]

Physical form: A white to off-white powder with pink casts at times.
Solubility Freely soluble in water.

Molecular formula: C_{25}H_{30}N_{2}O_{5}·HCl
Molecular weight: 474.98 g/mol

Quinapril hydrochloride complies with in-house specifications.

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance quinapril hydrochloride.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredients.

An appropriate specification is provided for quinapril hydrochloride, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.
Appropriate proof-of-structure data have been supplied for quinapril hydrochloride. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing quinapril hydrochloride to be physically and chemically stable drugs, and supporting an appropriate retest period.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients colloidal anhydrous silica, povidone K30, crospovidone, magnesium carbonate heavy, calcium sulphate dihydrate, water purified, magnesium stearate, opadry yellow.

All the ingredients with the exception of opadry yellow comply with their relevant European Pharmacopoeia monographs. Opadry yellow complies with in-house specifications.

None of the excipients used contain material of animal or human origin. The magnesium stearate contained in this product is sourced from vegetable origin and therefore no European Pharmacopoeia Certificates of suitability for TSE is required.

**Product development**

The objective of the development programme was to produce products that could be considered generic medicinal products of Accupro 5mg Tablets (Pfizer Limited).

The reference product used in the bioequivalence study (Acuitel 20mg Tablets) is qualitatively and quantitatively identical to the UK reference product.

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative dissolution and impurity profiles have been provided for the finished product versus the reference product Accupro 5mg Tablets (Pfizer Limited).

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on pilot scale batches of each strength of finished product and the results appear satisfactory. The applicant has committed to perform process validation on future commercial-scale batches.

**Finished product specification**

The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis for all working standards used have been provided and are satisfactory.
**Container-Closure System**
The product is packaged in blister packs composed of aluminium with aluminium foil lidding, packed into cartons. The product comes in sizes of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 112, 250, 300 and 500 tablets.

Specifications and certificates of analysis have been provided. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 2 years has been set, with storage conditions ‘Store below 25°C’, which is satisfactory.

**ADMINISTRATIVE**
**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SPC)**
These are pharmaceutically satisfactory.

**Labelling**
These are pharmaceutically satisfactory.

**Patient Information Leaflet (PIL)**
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA Form**
These are pharmaceutically satisfactory.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
PRECLINICAL ASSESSMENT

These applications for Quinapril 5mg, 10mg, 20mg and 40mg Tablets are submitted as abridged standard applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Accupro Tablets 5mg (PL 00018/0148), first authorised in the UK to Parke Davis and Company Limited in June 1989, which underwent a change of ownership in October 1997 to Warner Lambert (UK) Limited (PL 00019/0123). This underwent a further change of ownership to Pfizer Limited (PL 00057/0514) in August 2003.

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
To support the applications, the marketing authorisation holder has included a single bioequivalence study:

A randomised, open label, two-treatment, two-sequence, two-period, two-way crossover, single dose bioequivalence study comparing the pharmacokinetics of Quinapril 20mg Tablets (Test) versus Acuitel 20mg Tablets (Reference) under fasted conditions.

Blood sampling was performed pre-drug administration, during the study and up to 72 hours post dose in each treatment period. There was a washout period of 11 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

Geometric Least Mean Squares and 90% Confidence Interval

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters of Quinapril</th>
<th>AUC\textsubscript{0-t} (ng/ml/h)</th>
<th>AUC\textsubscript{0-\infty} (ng/ml/h)</th>
<th>C\textsubscript{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinapril:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>274 ± 104</td>
<td>280 ± 105</td>
<td>283 ± 138</td>
</tr>
<tr>
<td>Reference</td>
<td>260 ± 87</td>
<td>265 ± 87</td>
<td>252 ± 134</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>99.3 – 111.4</td>
<td>99.6 – 111.5</td>
<td>99.6 – 127.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters of Quinapril (active metabolite)</th>
<th>AUC\textsubscript{0-t} (ng/ml/h)</th>
<th>AUC\textsubscript{0-\infty} (ng/ml/h)</th>
<th>C\textsubscript{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinapril (active metabolite):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>4048 ± 892</td>
<td>4168 ± 894</td>
<td>1125 ± 265</td>
</tr>
<tr>
<td>Reference</td>
<td>3904 ± 1046</td>
<td>4024 ± 1043</td>
<td>1065 ± 251</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>100.7 – 107.0</td>
<td>100.5 – 106.8</td>
<td>100.7 – 111.1</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC\textsubscript{0-t}, AUC\textsubscript{0-\infty}, and C\textsubscript{max} for the metabolite Quinaprilat and AUC\textsubscript{0-t} and AUC\textsubscript{0-\infty} for Quinapril lie within 80-125% boundaries. The upper limit of the 90% confidence interval test/reference ratio of C\textsubscript{max} for Quinapril lies outside the 80 – 125% boundary. The applicant provided adequate justification for the widening of the C\textsubscript{max} confidence interval. The conclusion of bioequivalence was accepted, taking account of active metabolite data (Quinaprilat), relative activity and extent of exposure of the parent (Quinapril).
EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with those for the reference products and are satisfactory.

DISCUSSION
The applicant has satisfactorily demonstrated bioequivalence between the test and reference products.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that Quinapril Tablets can be considered as generic medicinal products to the originator products Accupro Tablets (Pfizer Limited). The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Quinapril 5mg, 10mg, 20mg and 40mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Quinapril 5mg, 10mg, 20mg and 40mg Tablets and the reference product. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the Quinapril 20mg Tablets can be extrapolated to the other strengths of 5mg, 10mg and 40mg Quinapril Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with quinapril is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
Quinapril 5mg, 10mg, 20mg and 40mg Tablets

PL 20092/0030-33

STEPS TAKEN FOR ASSESMENT

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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 9th October 2006.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 18th December 2006.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information on the quality sections of the dossier on 29th January 2007, 10th July 2007, 17th October 2007, 16th January 2008, 21st August 2008 and 22nd June 2009.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 21st September 2009.</td>
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Quinapril 5mg, 10mg, 20mg and 40mg Tablets

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**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Quinapril 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 mg tablet contains quinapril hydrochloride 5.416 mg equivalent to 5 mg Quinapril
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated Tablet
Quinapril Tablets 5mg are Yellow coloured, Oval shaped, film-coated tablets debossed with ‘5’ on one side and score line on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Hypertension
For the treatment of all grades of essential hypertension. Quinapril Tablet 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 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 80 mg/day.

Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of 2.5 mg of Quinapril Tablets is recommended in patients who are being treated with a diuretic. After this the dosage of Quinapril 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 usually maintained effectively on doses of 10-20 mg/day given with concomitant therapy. Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.

Severe Heart Failure
In the treatment of severe or unstable congestive heart failure, Quinapril 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 mmol/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.
Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.
Elderly/Renal Impairment (over 65 years of age)
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 and adolescents (under 18 years of age)
There is limited clinical trial experience of the use of quinapril in hypertensive children aged 5 years and above. There are no data regarding children below 5 years of age. Therefore its use in children and adolescents is not recommended.

4.3 CONTRAINDICATIONS
Quinapril Tablets are contraindicated in patients with hypersensitivity to any of the ingredients.
Quinapril Tablets are contraindicated in second and third trimesters of pregnancy (see sections 4.4 and 4.6)

Quinapril Tablets are contraindicated in patients with a history of angioedema related to previous treatment with ACE inhibitors.
Quinapril Tablets are contraindicated in patients with hereditary/idiopathic angioneurotic oedema.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Quinapril Tablets should not be used in patients with aortic stenosis or outflow obstruction.
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.

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 anti-hypertensive 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).

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 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.

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.

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.

Hypotension: Symptomatic hypotension was rarely seen in hypertensive patients treated with Quinapril 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 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 Tablets. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Quinapril Tablets. 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 on quinapril alone may have increased 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 Tablets 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.

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.

Non-steroidal anti-inflammatory drugs: 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 procaainamide: Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia.

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

Other hypertensive drugs: There may be an additive effect or potentiation.

Antacids: May decrease the bioavailability of Quinapril Tablets.

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

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 contra-indicated 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 anti-hypertensive 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 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 demonstrate very low concentration in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant the use of quinapril 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 case of an older infant the use of quinapril in the breastfeeding 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

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.
4.8 UNDESIRABLE EFFECTS

The following undesirable effects have been observed during treatment with quinapril and other ACE inhibitors with the following frequencies:

- 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 from the available data)

Psychiatric disorders:
- Uncommon: Sleep disorders, nervousness
- Rare: Depression, confusion

Nervous system disorders:
- Common: Dizziness
- Uncommon: Paraesthesia, somnolence
- Rare: disturbances of balance, Neuropathy

Eye Disorders:
- Rare: Amblyopia, vision disturbances

Ear and labyrinth disorders:
- Rare: Tinnitus

Cardiac disorders:
- Uncommon: Palpitations, asystole, chest pain, angina pectoris
- Rare: tachycardia, syncope, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage

Vascular disorders:
- Common: Hypotension
- Uncommon: postural hypotension

Blood and lymphatic disorders:
- Uncommon: Neutropenia,
- Rare: Agranulocytosis

Respiratory, thoracic and mediastinal disorders:
- Common: Cough
- Uncommon: sinusitis, pharyngitis, upper respiratory tract infection
- Rare: Bronchospam, worsening of asthma, dyspnoea, bronchitis, rhinitis
- Very rare: allergic alveolitis, anaphylactoid reaction

Gastrointestinal disorders:
- Common: Nausea, vomiting, diarrhoea
- Uncommon: Dyspepsia, abdominal pain, dry mouth or throat, flatulence
- Rare: Altered taste, constipation, pancreatitis, glossitis, ileus

Hepato-biliary disorders:
- Rare: Hepatic function disturbances.
- Very rare: cholestatic icterus, hepatitis

Skin and subcutaneous tissue disorders:
- Uncommon: Exanthema, pruritus, exfoliative dermatitis, rash, urticaria, increased perspiration
- Rare: erythema multiforme, Stevens Johnson syndrome, epidermic necrolysis, psoriasis-like efflorescences, alopecia, Pemphigus, photosensitivity
Muscloskeletal, connective tissue and bone disorders:
Rare: Myalgia, arthralgia, back pain

Renal and urinary disorders:
Uncommon: proteinuria
Rare: Impaired renal function, hyperkalaemia
Very Rare: kidney failure.

Reproductive system and breast disorders
Uncommon: Impotence.

General disorders:
Common: Headache, tiredness
Uncommon: Asthenia, vertigo, Angioedema (with swelling of face, lips, tongue, pharynx)

Rare cases of agranulocytosis have been reported, and also a syndrome including fever, serositis, vasculitis, myalgia, arthralgia/arthritis, positive ANA-titre, SR-elevation, eosinophilia, and leukocytosis, Gynaecomastia and vasculitis have been reported with other ACE-inhibitors and it cannot be excluded that these unwanted effects are group specific.

Laboratory values: Transient increases in serum creatinine and urea values have been reported, especially in association with concomitant therapy with diuretics. Slight decreases in haemoglobin and haematocrit values have been reported for other ACE-inhibitors. It cannot be excluded that these observations are group specific.

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 medical care.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC code: C09AA06
Pharmacotherapeutic group: Angiotensin-converting enzyme (ACE) inhibitor.

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.

In a randomised clinical trial using target doses of 2.5, 5, 10 and 20 mg of quinalapril, 112 children and adolescents with hypertension or high normal blood pressure over 8 weeks (2 weeks double blind and 6 weeks extension), a reduction in systolic blood pressure alone was noted across all treatment groups. The reduction in diastolic pressure overall, and for each group was similar to placebo in this group of subjects suggesting that a dose response effect was not established.
5.2 PHARMACOKINETIC PROPERTIES

Peak plasma quinapril tablets 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 tablets have 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. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril tablets. Studies in rats indicate that quinapril tablets 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 M/P (milk to plasma ratio) for quinapril was 0.12. Quinapril was not detected in milk after 4 hours after the dose. Quinalaprilat milk levels were undetectable (<5µg/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

Core
- Magnesium carbonate, Heavy
- Calcium Sulfate dihydrate
- Silica, Colloidal Anhydrous
- Crospovidone
- Povidone
- Magnesium Stearate
- Coating
- Polyvinyl alcohol
- Titanium dioxide (E171)
- Talc
- Lecithin
- Iron Oxide Yellow (E172)
- Xanthan gum

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Quinapril tablets are supplied in blister packs using aluminium as forming (base) material and aluminium foil as the lidding, which are further packed in cartons.

Packs of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 112, 250, 300 and 500 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

Any unused or waste material should be disposed of in accordance with local requirements.
MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court, Bexton Road,
Knutsford
Cheshire WA16 0PF
United Kingdom

MARKETING AUTHORISATION NUMBER(S)
PL 20092/0030

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/09/2009

DATE OF REVISION OF THE TEXT
21/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Quinapril 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 10 mg tablet contains quinapril hydrochloride 10.832 mg equivalent to 10 mg Quinapril
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated Tablet
Yellow coloured, capsule shaped, film-coated tablets debossed with ‘10’ on one side and scoreline on the other side.
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
Hypertension
For the treatment of all grades of essential hypertension. Quinapril Tablets are 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 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 80 mg/day.

Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of 2.5 mg of Quinapril Tablets is recommended in patients who are being treated with a diuretic. After this the dosage of Quinapril 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 usually maintained effectively on doses of 10-20 mg/day given with concomitant therapy. Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.

Severe Heart Failure
In the treatment of severe or unstable congestive heart failure, Quinapril 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 mmol/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.
Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.

Elderly/Renal Impairment (over 65 years of age)
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 and adolescents (under 18 years of age.)
There is limited clinical trial experience of the use of quinapril in hypertensive children aged 5 years and above. There are no data regarding children below 5 years of age. Therefore its use in children and adolescents is not recommended.

4.3 CONTRAINDICATIONS
Quinapril Tablets are contraindicated in patients with hypersensitivity to any of the ingredients.
Quinapril Tablets are contraindicated in second and third trimesters of pregnancy (see sections 4.4 and 4.6)
Quinapril Tablets are contraindicated in patients with a history of angioedema related to previous treatment with ACE inhibitors.
Quinapril Tablets are contraindicated in patients with hereditary/idiopathic angioneurotic oedema.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Quinapril Tablets should not be used in patients with aortic stenosis or outflow obstruction.
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.

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 anti-hypertensive 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).

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 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.
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.

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.

Hypotension: Symptomatic hypotension was rarely seen in hypertensive patients treated with Quinapril 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 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 Tablets. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Quinapril Tablets. 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 on quinapril alone may have increased 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 Tablets 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.
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.

Non-steroidal anti-inflammatory drugs: 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 hypertensive drugs: There may be an additive effect or potentiation.

Antacids: May decrease the bioavailability of Quinapril Tablets.

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

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 contra-indicated 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 anti-hypertensive 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 section 4.3 and 4.4).

Lactation

Limited pharmacokinetic data demonstrate very low concentration in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant the use of quinapril 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 case of an older infant the use of quinapril in the breastfeeding 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

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.
4.8 UNDESIRABLE EFFECTS
The following undesirable effects have been observed during treatment with quinapril and other ACE inhibitors with the following frequencies:

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 from the available data)

Psychiatric disorders:
Uncommon: Sleep disorders, nervousness
Rare: Depression, confusion

Nervous system disorders:
Common: Dizziness
Uncommon: Paraesthesia, somnolence
Rare: disturbances of balance, Neuropathy

Eye Disorders:
Rare: Amblyopia, vision disturbances

Ear and labyrinth disorders:
Rare: Tinnitus

Cardiac disorders:
Uncommon: Palpitations, asystole, chest pain, angina pectoris
Rare: tachycardia, syncope, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage

Vascular disorders:
Common: Hypotension
Uncommon: postural hypotension

Blood and lymphatic disorders
Uncommon: Neutropenia,
Rare: Agranulocytosis

Respiratory, thoracic and mediastinal disorders:
Common: Cough
Uncommon: sinusitis, pharyngitis, upper respiratory tract infection
Rare: Bronchospam, worsening of asthma, dyspnoea, bronchitis, rhinitis
Very rare: allergic alveolitis, anaphylactoid reaction

Gastrointestinal disorders:
Common: Nausea, vomiting, diarrhoea
Uncommon: Dyspepsia, abdominal pain, dry mouth or throat, flatulence
Rare: Altered taste, constipation, pancreatitis, glossitis, ileus

Hepato-biliary disorders:
Rare: Hepatic function disturbances.
Very rare: cholestatic icterus, hepatitis

Skin and subcutaneous tissue disorders:
Uncommon: Exanthema, pruritus, exfoliative dermatitis, rash, urticaria, increased perspiration
Rare: erythema multiforme, Stevens Johnson syndrome, epidermic necrosis, psoriasis-like effloresences, alopecia, Pemphigus, photosensitivity

Musculoskeletal, connective tissue and bone disorders:
Rare: Myalgia, arthralgia, back pain
Renal and urinary disorders:
Uncommon: proteinuria
Rare: Impaired renal function, hyperkalaemia
Very Rare: kidney failure.

Reproductive system and breast disorders
Uncommon: Impotence.

General disorders:
Common: Headache, tiredness
Uncommon: Asthenia, vertigo, Angioedema (with swelling of face, lips, tongue, pharynx)

Rare cases of agranulocytosis have been reported, and also a syndrome including fever, serositis, vasculitis, myalgia, arthralgia/arthritis, positive ANA-titre, SR-elevation, eosinophilia, and leukocytosis. Gynaecomastia and vasculitis have been reported with other ACE-inhibitors and it cannot be excluded that these unwanted effects are group specific.

Laboratory values: Transient increases in serum creatinine and urea values have been reported, especially in association with concomitant therapy with diuretics. Slight decreases in haemoglobin and haematocrit values have been reported for other ACE-inhibitors. It cannot be excluded that these observations are group specific.

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 medical care.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC code: C09AA06
Pharmacotherapeutic group: Angiotensin-converting enzyme (ACE) inhibitor.

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.
In a randomised clinical trial using target doses of 2.5, 5, 10 and 20 mg of quinalapril, 112 children and adolescents with hypertension or high normal blood pressure over 8 weeks (2 weeks double blind and 6 weeks extension), a reduction in systolic blood pressure alone was noted across all treatment groups. The reduction in diastolic pressure overall, and for each group was similar to placebo in this group of subjects suggesting that a dose response effect was not established.

5.2 PHARMACOKINETIC PROPERTIES

Peak plasma quinapril tablets 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 tablets have 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. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril tablets. Studies in rats indicate that quinapril tablets 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 M/P (milk to plasma ratio) for quinapril was 0.12. Quinapril was not detected in milk after 4 hours after the dose. Quinalaprilat milk levels were undetectable (<5µg/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

Core
Magnesium carbonate, Heavy
Calcium Sulfate dihydrate
Silica, Colloidal Anhydrous
Crospovidone
Povidone
Magnesium Stearate
Coating
Polyvinyl alcohol
Titanium dioxide (E171)
Talc
Lecithin
Iron Oxide Yellow (E172)
Xanthan gum

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.
6.5 NATURE AND CONTENTS OF CONTAINER
Quinapril tablets are supplied in blister packs using aluminium as forming (base) material and aluminium foil as the lidding, which are further packed in cartons.
Packs of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 112, 250, 300 and 500 tablets.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.
Any unused or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court, Bexton Road,
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20092/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/09/2009

10 DATE OF REVISION OF THE TEXT
21/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Quinapril 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 20 mg tablet contains quinapril hydrochloride 21.664 mg equivalent to 20 mg Quinapril
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated Tablet
Yellow colored, circular shaped, film-coated tablets debossed with ‘20’ on one side and scoreline on
the other side.
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
Hypertension
For the treatment of all grades of essential hypertension. Quinapril Tablets are 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 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 80 mg/day.

Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of
2.5 mg of Quinapril Tablets is recommended in patients who are being treated with a diuretic. After
this the dosage of Quinapril 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 usually
maintained effectively on doses of 10-20 mg/day given with concomitant therapy. Take either with
or without food. The dose should always be taken at about the same time of day to help increase
compliance.

Severe Heart Failure
In the treatment of severe or unstable congestive heart failure, Quinapril 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 mmol/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.
Take either with or without food. The dose should always be taken at about the same time of day to
help increase compliance.

Elderly/Renal Impairment (over 65 years of age)
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 and adolescents (under 18 years of age.)
There is limited clinical trial experience of the use of quinapril in hypertensive children aged 5 years and above. There are no data regarding children below 5 years of age. Therefore its use in children and adolescents is not recommended.

4.3 CONTRAINDICATIONS
Quinapril Tablets are contraindicated in patients with hypersensitivity to any of the ingredients. Quinapril Tablets are contraindicated in second and third trimesters of pregnancy (see sections 4.4 and 4.6)

Quinapril Tablets are contraindicated in patients with a history of angioedema related to previous treatment with ACE inhibitors.
Quinapril Tablets are contraindicated in patients with hereditary/idiopathic angioneurotic oedema.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Quinapril Tablets should not be used in patients with aortic stenosis or outflow obstruction.
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.

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 anti-hypertensive 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).

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 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.
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.

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.

Hypotension: Symptomatic hypotension was rarely seen in hypertensive patients treated with Quinapril 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 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 Tablets. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Quinapril Tablets. 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 on quinapril alone may have increased 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 Tablets 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.
**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.

**Non-steroidal anti-inflammatory drugs:** 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 hypertensive drugs:** There may be an additive effect or potentiation.

Antacids: May decrease the bioavailability of Quinapril Tablets.

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

### 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 contra-indicated 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 anti-hypertensive 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).

**Lactation**

Limited pharmacokinetic data demonstrate very low concentration in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant the use of quinapril 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 case of an older infant the use of quinapril in the breastfeeding 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

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.
4.8 UNDESIRABLE EFFECTS

The following undesirable effects have been observed during treatment with quinapril and other ACE inhibitors with the following frequencies:

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 from the available data)

Psychiatric disorders:
Uncommon: Sleep disorders, nervousness
Rare: Depression, confusion

Nervous system disorders:
Common: Dizziness
Uncommon: Paraesthesia, somnolence
Rare: disturbances of balance, Neuropathy

Eye Disorders:
Rare: Amblyopia, vision disturbances

Ear and labyrinth disorders:
Rare: Tinnitus

Cardiac disorders:
Uncommon: Palpitations, asystole, chest pain, angina pectoris
Rare: tachycardia, syncope, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage

Vascular disorders:
Common: Hypotension
Uncommon: postural hypotension

Blood and lymphatic disorders
Uncommon: Neutropenia,
Rare: Agranulocytosis

Respiratory, thoracic and mediastinal disorders;
Common: Cough
Uncommon: sinusitis, pharyngitis, upper respiratory tract infection
Rare: Bronchospasm, worsening of asthma, dyspnoea, bronchitis, rhinitis
Very rare: allergic alveolitis, anaphylactoid reaction

Gastrointestinal disorders:
Common: Nausea, vomiting, diarrhoea
Uncommon: Dyspepsia, abdominal pain, dry mouth or throat, flatulence
Rare: Altered taste, constipation, pancreatitis, glossitis, ileus

Hepato-biliary disorders:
Rare: Hepatic function disturbances.
Very rare: cholestatic icterus, hepatitis

Skin and subcutaneous tissue disorders:
Uncommon: Exanthera, pruritus, exfoliative dermatitis, rash, urticaria, increased perspiration
Rare: erythema multiforme, Stevens Johnson syndrome, epidermic necrolysis, psoriasis-like efflorescences, alopecia, Pemphigus, photosensitivity

Musculoskeletal, connective tissue and bone disorders:
Rare: Myalgia, arthralgia, back pain
Renal and urinary disorders:
Uncommon: proteinuria
Rare: Impaired renal function, hyperkalaemia
Very Rare: kidney failure.

Reproductive system and breast disorders
Uncommon: Impotence.

General disorders:
Common: Headache, tiredness
Uncommon: Asthenia, vertigo, Angioedema (with swelling of face, lips, tongue, pharynx)

Rare cases of agranulocytosis have been reported, and also a syndrome including fever, serositis, vasculitis, myalgia, arthralgia/arthritis, positive ANA titre, SR-elevation, eosinophilia, and leukocytosis, Gynaecomastia and vasculitis have been reported with other ACE-inhibitors and it cannot be excluded that these unwanted effects are group specific.

Laboratory values: Transient increases in serum creatinine and urea values have been reported, especially in association with concomitant therapy with diuretics. Slight decreases in haemoglobin and haematocrit values have been reported for other ACE-inhibitors. It cannot be excluded that these observations are group specific.

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 medical care.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC code: C09AA06
Pharmacotherapeutic group: Angiotensin-converting enzyme (ACE) inhibitor.

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.
In a randomised clinical trial using target doses of 2.5, 5, 10 and 20 mg of quinalapril, 112 children and adolescents with hypertension or high normal blood pressure over 8 weeks (2 weeks double blind and 6 weeks extension), a reduction in systolic blood pressure alone was noted across all treatment groups. The reduction in diastolic pressure overall, and for each group was similar to placebo in this group of subjects suggesting that a dose response effect was not established.

5.2 PHARMACOKINETIC PROPERTIES

Peak plasma quinapril tablets 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 tablets have 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. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril tablets. Studies in rats indicate that quinapril tablets 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 M/P (milk to plasma ratio) for quinapril was 0.12. Quinapril was not detected in milk after 4 hours after the dose. Quinalaprilat milk levels were undetectable (<5µg/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

Core
Magnesium carbonate, Heavy
Calcium Sulfate dihydrate
Silica, Colloidal Anhydrous
Crospovidone
Povidone
Magnesium Stearate
Coating
Polyvinyl alcohol
Titanium dioxide (E171)
Talc
Lecithin
Iron Oxide Yellow (E172)
Xanthan gum

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
6.5 NATURE AND CONTENTS OF CONTAINER
Quinapril tablets are supplied in blister packs using aluminium as forming (base) material and aluminium foil as the lidding, which are further packed in cartons.
Packs of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 112, 250, 300 and 500 tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.
Any unused or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court, Bexton Road,
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20092/0032

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/09/2009

10 DATE OF REVISION OF THE TEXT
21/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Quinapril 40mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 40 mg tablet contains quinapril hydrochloride 43.328 mg equivalent to 40 mg Quinapril
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Film-coated Tablet
Yellow coloured, capsule shaped, film-coated tablets debossed with ‘40’ on one side and plain on the other side.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Hypertension
For the treatment of all grades of essential hypertension. Quinapril Tablets are 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 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 80 mg/day.

Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of 2.5 mg of Quinapril Tablets is recommended in patients who are being treated with a diuretic. After this the dosage of Quinapril 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 usually maintained effectively on doses of 10-20 mg/day given with concomitant therapy. Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.

Severe Heart Failure
In the treatment of severe or unstable congestive heart failure, Quinapril 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 mmol/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.
Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.

Elderly/Renal Impairment (over 65 years of age)
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 and adolescents (under 18 years of age.)
There is limited clinical trial experience of the use of quinapril in hypertensive children aged 5 years and above. There are no data regarding children below 5 years of age. Therefore its use in children and adolescents is not recommended.

4.3 CONTRAINDICATIONS
Quinapril Tablets are contraindicated in patients with hypersensitivity to any of the ingredients.
Quinapril Tablets are contraindicated in second and third trimesters of pregnancy (see sections 4.4 and 4.6)

Quinapril Tablets are contraindicated in patients with a history of angioedema related to previous treatment with ACE inhibitors.
Quinapril Tablets are contraindicated in patients with hereditary/idiopathic angioneurotic oedema.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Quinapril Tablets should not be used in patients with aortic stenosis or outflow obstruction.
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.

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 anti-hypertensive 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).

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.

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**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.

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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 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.

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**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 on quinapril alone may have increased serum potassium levels.

When administered concomitantly, quinapril may reduce the hypokalaemia induced by thiazide diuretics.

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**Other hypertensive drugs:** There may be an additive effect or potentiation.

**Antacids:** May decrease the bioavailability of Quinapril Tablets.

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

### 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 contra-indicated 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 anti-hypertensive 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.

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**Lactation**

Limited pharmacokinetic data demonstrate very low concentration in breast milk (see section 5.2). Although these concentrations seem to be clinically irrelevant the use of quinapril 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 case of an older infant the use of quinapril in the breastfeeding 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

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.
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The following undesirable effects have been observed during treatment with quinapril and other ACE inhibitors with the following frequencies:

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Uncommon (≥ 1/1,000, to <1/100),
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Uncommon: Sleep disorders, nervousness
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Uncommon: Paraesthesia, somnolence
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Uncommon: Palpitations, asystole, chest pain, angina pectoris
Rare: tachycardia, syncope, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage

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Common: Hypotension
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Blood and lymphatic disorders
Uncommon: Neutropenia,
Rare: Agranulocytosis

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Very rare: cholestatic icterus, hepatitis

Skin and subcutaneous tissue disorders:
Uncommon: Exantheme, pruritus, exfoliative dermatitis, rash, urticaria, increased perspiration
Rare: erythema multiforme, Stevens Johnson syndrome, epidermic necrolysis, psoriasis-like efflorescences, alopecia, Pemphigus, photosensitivity

Musculoskeletal, connective tissue and bone disorders:
Rare: Myalgia, arthralgia, back pain
Renal and urinary disorders:
Uncommon: proteinuria
Rare: Impaired renal function, hyperkalaemia
Very Rare: kidney failure.

Reproductive system and breast disorders
Uncommon: Impotence.

General disorders:
Common: Headache, tiredness
Uncommon: Asthenia, vertigo, Angioedema (with swelling of face, lips, tongue, pharynx)

Rare cases of agranulocytosis have been reported, and also a syndrome including fever, serositis, vasculitis, myalgia, arthralgia/arthritis, positive ANA-titre, SR-elevation, eosinophilia, and leukocytosis, Gynaecomastia and vasculitis have been reported with other ACE-inhibitors and it cannot be excluded that these unwanted effects are group specific.

Laboratory values: Transient increases in serum creatinine and urea values have been reported, especially in association with concomitant therapy with diuretics. Slight decreases in haemoglobin and haematocrit values have been reported for other ACE-inhibitors. It cannot be excluded that these observations are group specific.

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 medical care.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
ATC code: C09AA06
Pharmacotherapeutic group: Angiotensin-converting enzyme (ACE) inhibitor.

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.
In a randomised clinical trial using target doses of 2.5, 5, 10 and 20 mg of quinalapril, 112 children and adolescents with hypertension or high normal blood pressure over 8 weeks (2 weeks double blind and 6 weeks extension), a reduction in systolic blood pressure alone was noted across all treatment groups. The reduction in diastolic pressure overall, and for each group was similar to placebo in this group of subjects suggesting that a dose response effect was not established.

5.2 PHARMACOKINETIC PROPERTIES

Peak plasma quinapril tablets 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 tablets have 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.

Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril tablets. Studies in rats indicate that quinapril tablets 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 M/P (milk to plasma ratio) for quinapril was 0.12. Quinapril was not detected in milk after 4 hours after the dose. Quinalaprilat milk levels were undetectable (<5µg/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

Core
Magnesium carbonate, Heavy
Calcium Sulfate dihydrate
Silica, Colloidal Anhydrous
Crospovidone
Povidone
Magnesium Stearate
Coating
Polyvinyl alcohol
Titanium dioxide (E171)
Talc
Lecithin
Iron Oxide Yellow (E172)
Xanthan gum

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
6.5 NATURE AND CONTENTS OF CONTAINER
Quinapril tablets are supplied in blister packs using aluminium as forming (base) material and aluminium foil as the lidding, which are further packed in cartons. Packs of 1, 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 112, 250, 300 and 500 tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements. Any unused or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court, Bexton Road, Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20092/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/09/2009

10 DATE OF REVISION OF THE TEXT
21/09/2009
PATIENT INFORMATION LEAFLET
QUINAPRIL 5mg, 10mg, 20mg AND 40mg TABLETS
QUINAPRIL HYDROCHLORIDE

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed on this leaflet, please tell your doctor or pharmacist.

In This Leaflet:
1. What these tablets are and what they are used for.
2. Before you take these tablets.
3. How to take these tablets.
4. Possible side effects.
5. How to store these tablets.
6. Further information.

1. WHAT THESE TABLETS ARE AND WHAT THEY ARE USED FOR

The active ingredient in Quinapril Tablets is quinapril (present as quinapril hydrochloride). This belongs to a group of medicines called angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors work by widening blood vessels in the body, which can reduce the pressure in the vessels.

For the other ingredients in Quinapril Tablets, (see section 6.)

Quinapril is an ACE inhibitor used to treat high blood pressure (hypertension) and to help treat heart failure. Quinapril is effective alone or together with water tablets (diuretics) in patients with hypertension. Quinapril can also be used for the treatment of heart failure when given together with a diuretic and/or cardiac glycoside such as digoxin.

Treatment of heart failure with quinapril should always be started under close medical supervision.

2. BEFORE YOU TAKE THESE TABLETS

Do not take Quinapril Tablets if:

- you are allergic (hypersensitive) to quinapril, any other ACE inhibitor or any of the other ingredients of these tablets
- you are more than 3 months pregnant. (It is also better to avoid quinapril tablets in early pregnancy – see pregnancy section.)
- you have taken an ACE inhibitor before and had an allergic reaction to it resulting in swelling of the face, lips, tongue and/or throat with difficulty in swallowing or breathing or you or any member of your blood relatives have suffered a similar allergic reaction for any reason in the past.
- you suffer from a severe allergic skin reaction called hereditary/idiopathic angioneurotic oedema where itchy swellings erupt on your face, hands, genital areas and mouth.

If you think any of these apply to you, do not use any of these tablets. Talk to your doctor first and follow the advice given to you.

Take special care with these tablets

Tell your doctor if:

- you think you are (or might become) pregnant. Quinapril tablets are not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section)
- you have aortic stenosis (narrowing of the main blood vessel from the heart)
- you have kidney disease
- you are using a haemodialysis machine (an artificial kidney)
- you are taking diuretics (water tablets)
- you have collagen vascular disease such as dermatomyositis, (connective-tissue disease that is characterized by inflammation of the muscles and the skin) lupus erythematosus (SLE condition which causes joint pain, skin rashes, and fever) or polyarthritis nodosa (inflammation of the arteries)
- you are having, or about to have, low density lipoprotein apheresis treatment (removal of cholesterol from your blood by machine)
- you are having, or about to have, desensitisation treatment i.e. to reduce the effects of an allergy to a bee or wasp sting
- you have had a recent bout of diarrhoea and/or vomiting
- you have narrowing or blockage of the blood vessels leading to the kidneys

Using other medicines

The following medicinal products may interact with quinapril, either by increasing or decreasing its effect.

- Tetracycline-antibiotic
- Blood pressure lowering medicines (captopril, enalapril, lisinopril)
- Antacids-medicines to treat heart burn or indigestion
- Antidiabetic drugs (oral agents e.g. glibenclamide and insulin)
- Non steroidal anti-inflammatory drugs e.g. aspirin or ibuprofen
- Lithium supplements used for certain mental illns
- Potassium supplements, potassium-containing salt substitutes
- Diuretics (water tablets)
- Anaesthetic agents used in surgery
- Steroids (hydrocortisone, dexamethasone or prednisolone)
- ACTH (tetraoestor)
- Procarbamide (for irregular heart beat)
- Cyto-static drugs to treat cancer
- Immunosuppressants such as cyclosporin
- Allopurinol for gout
- Sympathomimetics found in asthma medication and cough remedies
- Sedatives

You should not drink alcohol whilst you are taking Quinapril as this can cause hypotension (low blood pressure)

Taking these tablets with food and drink

Quinapril tablets can be taken with or without food.

Pregnancy and breast-feeding

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking quinapril tablets before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of quinapril tablets. Quinapril tablets are not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. Breast-feeding newborn babies (first few weeks after birth), and especially premature babies, is not recommended whilst taking quinapril tablets.
In the case of an older baby your doctor should advise you on the benefits and risks of taking quinapril tablets whilst breast-feeding, compared with other treatments.

Driving and using machines
Quinapril Tablets may cause dizziness and/or tiredness and if you are affected you should not drive or operate any machines or tools.

If you take more these tablets than you should
If you or someone else take(s) too many tablets all together, contact your nearest hospital casualty department / your doctor immediately / a poison centre. You may feel particularly light-headed or faint, your heart rate may slow down and your skin may feel cold and clammy.

3. HOW TO TAKE THESE TABLETS
Always take these tablets exactly as your doctor has told you to. You should check with your doctor or pharmacist if you are not sure.
These tablets are usually taken once or twice a day.
For hypertension (high blood pressure) the usual starting dose is 10 mg, which may be increased to 20 to 40 mg a day.
For heart failure, or hypertension in combination with a water tablet (diuretic) and/or cardiac glycoside such as digoxin, the usual starting dose is 2.5 mg, which may be increased up to 10 to 40 mg a day.
Swallow the tablets whole with a drink of water. Do not chew them. It is best to take your tablets approximately the same time each day.

Elderly (over 65 years of age) / kidney problems
In elderly patients and in patients with kidney problems, the usual starting dose for blood pressure is 2.5 mg which may be slowly increased.

Children and adolescents (under 18 years of age)
Due to limited experience, Quinapril tablets are not recommended in children and adolescents.

If you forget to take these tablets
If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking these tablets
Do not stop taking these tablets, without asking your doctor or pharmacist.
If you have any further questions about taking this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines Quinapril Tablets can cause side effects, although not everybody gets them
If you develop any of the following symptoms, contact a doctor immediately:
- You get a swollen face, tongue and / or throat, severe reddening of the skin (hives) and / or have difficulty in swallowing and/ or breathing (angioedema).

The following undesirable effects have been observed during treatment with quinapril and other ACE inhibitors with the following frequencies:
Common (affecting at least or more than 1 in 100 patients treated but less than 1 in 10 patients treated):
- Dizziness
- Low blood pressure (Hypotension)
- Cough
- Nausea
- Vomiting
- Diarrhoea
- Headache
- Tiredness

Uncommon (affecting at least or more than 1 in 1000 patients treated but less than 1 in 100 Patients treated):
- Sleep disorders
- Nervousness
- Tingling or numbness in the hands or feet
- Sleepiness
- feeling your heartbeat (Palpitations)
- asymptomatic which is when the heart suddenly stops
- Chest pain (angina)
- low blood pressure which is felt on standing for example feeling light-headed when you stand up (Postural hypotension)
- reduction in white blood cell count seen with blood tests or through getting frequent infections
- inflammation of sinuses (Sinusitis)
- inflammation of pharynx (pharyngitis)
- chest infection
- indigestion
- Abdominal pain
- Dry mouth or throat
- Wind
- Rash
- Itching
- Exfoliative dermatitis
- Hives
- increased sweating
- Raised amount of proteins in the urine (proteinuria)
- Loss of sexual performance in a man (Impotence)
- Weakness
- Vertigo (spinning sensation)
- Angioedema (a serious allergic reaction with swelling of face, lips, tongue)

Rare (affecting more than 1 in 10,000 patients treated but less than 1 in 1000 patients treated):
- Depression
- Confusion
- Disturbances of balance
- nerve damage
- severe reduction in the number of white blood cells which makes infection more likely (agranulocytosis)
- poor vision in one eye (ambyopia)
- Vision disturbances
- Ringing in the ears
- Faster heart beat
- Fainting
- heart attack
- Transient periods where blood stops flowing in your body. For example, stroke
- Difficulty in breathing
- Worsening of asthma
- shortness of breath
- Bronchitis
- runny nose
- Taste disturbances
- Constipation
- Pancreatitis (inflammation of the pancreas)
- Glossitis (inflammation of the mouth)
- Partial or complete non-mechanical blockage of large and or small intestine (ileus)
- Liver problems
- Erythema multiforme (a painful reddening of the skin with lumps and blisters)
- Stevens Johnson syndrome (a severe and widespread reddening of the skin with blistering)
- Epidemic necrolysis ( rash involving reddening, swelling and peeling of the skin, it resembles severe burns)
- Silver plaques resembling psoriasis
- hair loss (alopecia)
- a very rare but serious blistering of the skin (pemphigus)
- Sensitivity to light
- muscle pain
- Joint pain
- back pain
- Kidney problems
- High blood potassium levels measured by a blood test.

Very rare (affecting less than 1 in 10000 patients treated)
- allergic lung disorder (Allergic alveolitis)
- serious allergic reaction which causes difficulty in breathing. (angioedema)
- jaundice due to impaired excretion of bile pigment (cholestatic icterus)
- Inflammation of the liver (Hepatitis)
- Kidney failure
- Blood disorders may occur with symptoms of pallor, fever or chills, sore throat and ulcers in your mouth or throat.

The following side-effects have been reported with other ACE inhibitors and may also occur with Quinapril tablets:
- breast enlargement in males
- low haemoglobin in your blood which can cause anaemia
- raised creatinine and urea blood levels (used to test your kidney function)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE THESE TABLETS
Keep out of the reach and sight of children.
Store below 25°C Do not use these tablets after the expiry date, which is stated on the pack.
The expiry date refers to the last day of that month.

Disposal
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
6. **FURTHER INFORMATION**

**What these Tablets contains**
The active substance is quinapril (as hydrochloride).

The other ingredients are:
Heavy Magnesium carbonate, Calcium sulfate dihydrate, Colloidal anhydrous silica, Crospovidone, Povidone, Magnesium stearate.
The coating of Quinapril tablets contains polyvinyl alcohol, titanium dioxide (E171), talc, lecithin, iron oxide yellow (E172) and xanthan gum.

**What these tablets look like and the contents of the pack**
Quinapril Tablets are available in four strengths

**Quinapril 5 mg Tablets**
- Yellow coloured, Oval shaped, film-coated tablets debossed with ‘5’ on one side and scoreline on the other side.
  
The score line facilitates breaking of the tablet into equal halves.

**Quinapril 10 mg Tablets**
- Yellow coloured, capsule shaped, film-coated tablets debossed with ‘10’ on one side and scoreline on the other side.
  
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

**Quinapril 20 mg Tablets**
- Yellow coloured, circular, film-coated tablets debossed with ‘20’ on one side and scoreline on the other side.
  
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

**Quinapril 40 mg Tablets**
- Yellow coloured, capsule shaped, film-coated tablets debossed with ‘40’ on one side and plain on the other side.

Quinapril Tablets are available in blister packs of 28 tablets.

**Marketing Authorisation Holder and Manufacturer**
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire, WA16 0FF
United Kingdom

This leaflet was last approved in June 2009
Quinapril 5 mg Tablets
Quinapril (as hydrochloride)

28 Tablets
Lupin (Europe) Ltd.

Each tablet contains: 5 mg of quinapril (as hydrochloride).
Dosage: For oral use. Read the package leaflet before use.
Storage: Store below 25°C.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Quinapril 10 mg Tablets

Each tablet contains: 10 mg of quinapril (as hydrochloride).

Dosage: For oral use. Read the package leaflet before use.

Storage: Store below 25°C.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Quinapril 10 mg Tablets
28 Tablets

Please affix dispensary label here
Quinapril 40 mg Tablets

Each tablet contains: 40 mg of quinapril (as hydrochloride).
Dosage: For oral use. Read the package leaflet before use.
Storage: Store below 25°C.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Please affix dispensary label here