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

PL 18909/0151-4

UKPAR

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

PL 18909/0151-4

LAY SUMMARY

On 29th September 2009, the MHRA granted Arrow Generics Limited Marketing Authorisations (licences) for Quinapril 5mg, 10mg, 20mg and 40mg Tablets (PL 18909/0151-4).

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 18909/0151-4

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Arrow Generics Limited Marketing Authorisations for the medicinal products Quinapril 5mg, 10mg, 20mg and 40mg Tablets (PL 18909/0151-4) on 29th 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 Acupril 20mg Tablet, first authorised in the Netherlands to Pfizer B.V. in August 1990.

Quinapril hydrochloride is an angiotensin converting enzyme inhibitor used for treatment of heart failure and hypertension. Daily doses of up to 40mg (heart failure) and 80mg (hypertension) may be administered once or twice daily. Initial doses of 2.5mg daily are recommended if used concomitantly with diuretics (in hypertension), in heart failure and in the elderly and those with renal impairment. The brand leader does not market a 2.5mg strength tablet.

Quinapril is a prodrug and is de-esterified in the liver to the major active metabolite, quinaprilat. The bioavailability of quinapril is about 60% and the half-life of quinaprilat is about 3 hours.
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:

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 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 magnesium carbonate (heavy), crospovidone, magnesium stearate, hydroxypropylcellulose.

The tablet coating for all tablet strengths contain: of poly (ethyl acrylate, methyl methacrylate), macrogol 6000, titanium dioxide (E-171) and talc.

The colorant excipient varies depending on tablet strength:
- The yellow 5mg tablets contain yellow iron oxide (E-172)
- The white 10mg tablets contain no extra excipient.
- The yellow 20mg tablets contain yellow iron oxide (E-172)
- The red 40mg tablets contain red iron oxide (E-172)

All the ingredients with the exception of hydroxypropylcellulose, eudragit E 12.5% and the colorant excipients comply with their relevant European Pharmacopoeia monographs.

Hydroxypropylcellulose complies with the United States pharmacopoeia. Eudragit E 12.5% and the colorant excipients comply with in-house specifications.

None of the excipients used contain material of animal or human origin. The Certificate of Analysis from the magnesium stearate supplier confirms that magnesium stearate is of vegetable origin.

**Product development**
The objective of the development programme was to produce products that could be considered generic medicinal products of Acupril 20mg Tablet (Pfizer B.V.).

The reference products used in the bioequivalence studies (Acuprel 5mg and 40mg Tablets) are qualitatively and quantitatively identical to the UK reference products.

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 Acupril 20mg Tablet (Pfizer B.V.).

**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 three pilot scale batches of each strength of finished product and the results appear satisfactory. The applicant has committed to perform process validation on the first three 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, polyamide and polyvinyl chloride. The product comes in a pack size of 28 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, shelf lives of 2 years for the 5mg and 10mg strengths and 3 years for the 20mg and 40mg strengths have been set, with storage conditions ‘Store below 25°C’ and ‘Store in original package’, 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.

**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 Acupril 20mg Tablet, first authorised in the Netherlands to Pfizer B.V. in August 1990.

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 two bioequivalence studies:

Study 1
A randomised, open label, two-period, two-way crossover, single centre bioequivalence study comparing the pharmacokinetics of Quinapril 40mg Tablets (Test) versus Acuprel 40mg Tablets (Reference) in healthy volunteers.

Blood sampling was performed 15 times up to 24 hours post dose in each treatment period. There was a washout period of 7-14 days (variable between two studies). 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

Pharmacokinetic parameters of Quinapril

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-\infty} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinapril:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>393.11 ± 173.45</td>
<td>402.52 ± 173.90</td>
<td>408.28 ± 251.1</td>
</tr>
<tr>
<td>Reference</td>
<td>383.23 ± 144.46</td>
<td>390.44 ± 144.03</td>
<td>363.03 ± 168.58</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>94.15 – 108.84</td>
<td>94.95 – 109.51</td>
<td>109.97 – 117.19</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters of Quinaprilat (active metabolite)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-\infty} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinaprilat (active metabolite):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>4197.8 ± 972.2</td>
<td>4294.37 ± 972.2</td>
<td>1206.51 ± 344.85</td>
</tr>
<tr>
<td>Reference</td>
<td>3920.8 ± 1025.75</td>
<td>4021.43 ± 1054.68</td>
<td>1093.89 ± 296.7</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>107.76</td>
<td>107.5</td>
<td>109.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-\infty} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>103.6 – 112.32</td>
<td>103.2 – 111.99</td>
<td>103.23 – 117.19</td>
</tr>
</tbody>
</table>

Study 2
A randomised, open label, two-period, two-way crossover, single centre bioequivalence study comparing the pharmacokinetics of Quinapril 5mg Tablets (Test) versus Acuprel 5mg Tablets (Reference) in healthy volunteers.

Blood sampling was performed 15 times up to 24 hours post dose in each treatment period. There was a washout period of 7-14 days (variable between two studies). 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
Pharmacokinetic parameters of Quinapril

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinapril:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>48.50 ± 18.4</td>
<td>50.58 ± 19.3</td>
<td>39.58 ± 17.3</td>
</tr>
<tr>
<td>Reference</td>
<td>51.12 ± 21.8</td>
<td>53.02 ± 21.77</td>
<td>38.78 ± 22.45</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>89.33 – 104.94</td>
<td>89.5 – 104.6</td>
<td>95.5 – 119.9</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters of Quinaprilat (active metabolite)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinaprilat (active metabolite):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>336.7 ± 90.2</td>
<td>352.7 ± 92.0</td>
<td>86.33 ± 23.9</td>
</tr>
<tr>
<td>Reference</td>
<td>353.3 ± 111.57</td>
<td>369.2 ± 112.8</td>
<td>92.19 ± 32.6</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>90.9 – 102.79</td>
<td>91.03 – 102.68</td>
<td>87.68 – 103.8</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0,t} and C_{max} for quinapril and its metabolite lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in both studies.

**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 Acuprel Tablets. 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 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 5mg and 40mg Tablets can be extrapolated to the other strengths of 10mg and 20mg 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 18909/0151-4**

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**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 12th June 2003.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 3rd May 2006.</td>
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<td>3</td>
<td>Following assessment of the applications, the MHRA requested further information on the quality sections of the dossier on 3rd May 2006</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality sections of the dossier on 27th August 2006.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 9th April 2008.</td>
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Quinapril 5mg, 10mg, 20mg and 40mg Tablets

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<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 Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains quinapril hydrochloride equivalent to 5 mg quinapril.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Yellow, round, biconvex, with one line dividing it in half.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
- Hypertension
  For the treatment of all grades of essential hypertension. Quinapril 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 should always be initiated under close medical supervision.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For oral use
Adult:
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.
Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.

Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of 2.5 mg of Quinapril is recommended in patients who are being treated with a diuretic. After this the dosage of Quinapril 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 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 furosemide) or on multiple diuretic therapy, have hypovolaemia, hypotensionaemia (serum sodium < 130 mgEq/l) or systolic blood pressure < 90 mm Hg, are on high dose vasodilator therapy, have a serum creatinine > 150 µmol/l or are aged 70 years or over.

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

Children
(6-12 years)
Not recommended. Safety and efficacy in children have not been established
4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Quinapril 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.

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.

Hypotension:
Symptomatic hypotension was rarely seen in hypertensive patients treated with quinapril 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 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. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Quinapril. If discontinuation of the diuretic is not possible, medical supervision should be provided for up to two hours following administration of the initial dose.

**Agents increasing serum potassium:** Concomitant treatments with potassium sparing diuretics, potassium supplements or potassium salts should be used with caution and with appropriate monitoring of serum potassium. As with other ACE inhibitors, patients 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 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 antihypertensive drugs:** There may be an additive effect or potentiation.

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

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

Pregnancy: Quinapril is contraindicated throughout pregnancy. Quinapril has been shown to be foetotoxic in rabbits. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the foetus, limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios.

Should a woman become pregnant while receiving Quinapril, the drug should be discontinued as soon as possible. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If oliguria occurs, attention should be directed towards support of blood pressure and renal perfusion.

Lactation: Quinapril should not be used in nursing mothers.

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 most frequent adverse reactions in controlled clinical assays were: headache (7.2%), dizziness (5.5%), rhinitis (3.2%), coughing (3.9%), fatigue (3.5%), nausea or vomiting (2.8%) and myalgia (2.2%). Coughing is not productive, persistent and it is solved after discontinuing the treatment. The discontinuation of the treatment due to adverse reactions was only necessary in 5.2% of the patients treated with quinapril in controlled clinical assays.

Other adverse reactions present in more than 1% in patients treated with quinapril, with or without diuretics in controlled clinical assays were: diarrhoea (2.0%), chest pain (2.0%), upper respiratory tract infection (2.0%), abdominal pain (1.9%), viral infection (1.8%), dyspepsia (1.6%), dyspnoea (1.5%), back pain (1.4%), asthenia (1.3%), pharyngitis (1.3%), insomnia (1.3%), hypotension (1.1%), sinusitis (1.1%), paraesthesia (1.1%) and bronchitis (1.0%).

Reasonable, possible or definitive related or uncertain related adverse reactions with a frequency between 0.5% and 1% (except those mentioned above) in patients treated with quinapril (with or without diuretics) in controlled and uncontrolled clinical assays and in less frequent adverse events observed in clinical assays or post-commercialization experience were the following:

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

Gastro-intestinal: Flatulence, dry mouth, pancreatitis.

Nervous/psychiatric: Somnolence, dizziness, depression, nervousness.

Skin: Pruritus, rash, epidermic necrolysis, alopecia, urticaria.

Urogenital: Impotence, urinary tract infections.

Others: Oedema, arthralgia, amblyopia, anaemia.

Rare reactions (<0.5%): angioedema was described in 0.1% of cases (see Warnings and Precautions and Contra-indications). Even though cases of eosinophilic pneumonitis, hepatitis or hepatic failure have been reported with the use of other ACE inhibitors, in the case of quinapril these pathologies have been very infrequent.

Laboratory finds: Seldom agranulocytosis and neutropenia have been described uncertainly related to the use of quinapril (see Warnings and Precautions)

Hyperkalaemia: see Warnings and Precautions

Creatinine and BUN: Increases in blood urea and plasma creatinine (1.25 times the normal considered value) were observed in both cases in 2% of patients treated with quinapril as monotherapy.
4.9 OVERDOSE
No data are available with respect to overdosage in humans. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion.
Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.
Treatment is symptomatic and supportive consistent with established level of care.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Quinapril is rapidly de-esterified to quinaprilat (quinapril diacid, the principal metabolite) which is a potent angiotensin-converting enzyme (ACE) inhibitor (ATC Code: C09AA06).
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 10-40mg of quinapril to patients with mild to severe hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate.

Antihypertensive activity commences within one hour with peak effects usually achieved by two to four hours after dosing. Achievement of maximum blood pressure lowering effects may require two weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained in most patients throughout the 24-hour dosing interval and continue during long term therapy.

5.2 PHARMACOKINETIC PROPERTIES
Peak plasma Quinapril concentrations are observed within 1 hour of oral administration. The extent of absorption is approximately 60%, and is not influenced by food. Following absorption, Quinapril is de-esterified to its major active metabolite, quinaprilat, and to minor inactive metabolites.

Quinapril has an apparent half-life of approximately one hour. Peak plasma quinaprilat concentrations are observed approximately 2 hours following an oral dose of quinapril. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of 3 hours. In patients with renal insufficiency and creatinine clearance of ≤ 40 ml/min, peak and trough quinaprilat concentrations increase, time to peak concentration increases, apparent half-life increases, and time to steady state may be delayed. The elimination of quinaprilat is also reduced in elderly patients (> 65 years) and correlates well with the impaired renal function which frequently occurs in the elderly.

Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

5.3 PRECLINICAL SAFETY DATA
The results of the preclinical tests do not add anything of further significance to the prescriber.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Magnesium carbonate, Heavy
Crospovidone
Magnesium stearate
Hydroxypropylcellulose
Coating:
Poly (ethyl acrylate, methyl methacrylate)
Macrogol 6000
Yellow iron oxide (E-172)
Titanium dioxide (E-171)
Talc

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.
Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Quinapril 5mg Tablets are supplied in a pack of 28 tablets.
Aluminium/Aluminium-Polyamide-PVC blister strip.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special instructions needed.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way,
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0151

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/09/2009

10 DATE OF REVISION OF THE TEXT
29/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Quinapril 10 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains quinapril hydrochloride equivalent to 10 mg quinapril.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White, round, biconvex, with one line dividing it in half.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
• Hypertension
  For the treatment of all grades of essential hypertension. Quinapril 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 should always be initiated under close medical supervision.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For oral use
Adult:
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.
  Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.

  Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of 2.5 mg of Quinapril is recommended in patients who are being treated with a diuretic. After this the dosage of Quinapril 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 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 furosemide) or on multiple diuretic therapy, have hypovolaemia, hyponatraemia (serum sodium < 130 mgEq/l) or systolic blood pressure < 90 mm Hg, are on high dose vasodilator therapy, have a serum creatinine > 150 µ mol/l or are aged 70 years or over.

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

Children
(6-12 years)
Not recommended. Safety and efficacy in children have not been established

4.3 CONTRAINDICATIONS
• Quinapril is contraindicated in patients with hypersensitivity to any of the ingredients.
• Quinapril is contraindicated throughout pregnancy (see section 4.6),
• Quinapril is contraindicated in nursing mothers.
• Quinapril is contraindicated in patients with a history of angioedema related to previous treatment with ACE inhibitors.
• Quinapril is contraindicated in patients with hereditary/idiopathic angioneurotic oedema.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Quinapril 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.

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.

Hypotension:
Symptomatic hypotension was rarely seen in hypertensive patients treated with quinapril 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 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. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Quinapril. If discontinuation of the diuretic is not possible, medical supervision should be provided for up to two hours following administration of the initial dose.

**Agents increasing serum potassium:** Concomitant treatments with potassium sparing diuretics, potassium supplements or potassium salts should be used with caution and with appropriate monitoring of serum potassium. As with other ACE inhibitors, patients 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 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 antihypertensive drugs:** There may be an additive effect or potentiation.

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

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

### 4.6 PREGNANCY AND LACTATION

**Pregnancy:** Quinapril is contraindicated throughout pregnancy. Quinapril has been shown to be foetotoxic in rabbits. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure,
skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the foetus, limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios.

Should a woman become pregnant while receiving Quinapril, the drug should be discontinued as soon as possible. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If oliguria occurs, attention should be directed towards support of blood pressure and renal perfusion.

Lactation: Quinapril should not be used in nursing mothers.

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 most frequent adverse reactions in controlled clinical assays were: headache (7.2%), dizziness (5.5%), rhinitis (3.2%), coughing (3.9%), fatigue (3.5%), nausea or vomiting (2.8%) and myalgia (2.2%). Coughing is not productive, persistent and it is solved after discontinuing the treatment. The discontinuation of the treatment due to adverse reactions was only necessary in 5.2% of the patients treated with quinapril in controlled clinical assays.

Other adverse reactions present in more than 1% in patients treated with quinapril, with or without diuretics in controlled clinical assays were: diarrhoea (2.0%), chest pain (2.0%), upper respiratory tract infection (2.0%), abdominal pain (1.9%), viral infection (1.8%), dyspepsia (1.6%), dyspnoea (1.5%), back pain (1.4%), asthenia (1.3%), pharyngitis (1.3%), insomnia (1.3%), hypotension (1.1%), sinusitis (1.1%), paraesthesia (1.1%) and bronchitis (1.0%).

Reasonable, possible or definitive related or uncertain related adverse reactions with a frequency between 0.5% and 1% (except those mentioned above) in patients treated with quinapril (with or without diuretics) in controlled and uncontrolled clinical assays and in less frequent adverse events observed in clinical assays or post-commercialization experience were the following:

Cardiovascular: Palpitations, tachycardia, syncope, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage.
Gastro-intestinal: Flatulence, dry mouth, pancreatitis.
Nervous/psychiatric: Somnolence, dizziness, depression, nervousness.
Skin: Pruritus, rash, epidermic necrolysis, alopecia, urticaria.
Urogenital: Impotence, urinary tract infections.
Others: Oedema, arthralgia, amblyopia, anaemia.

Rare reactions (<0.5%): angioedema was described in 0.1% of cases (see Warnings and Precautions and Contra-indications). Even though cases of eosinophilic pneumonitis, hepatitis or hepatic failure have been reported with the use of other ACE inhibitors, in the case of quinapril these pathologies have been very infrequent.

Laboratory finds: Seldom agranulocytosis and neutropenia have been described uncertainly related to the use of quinapril (see Warnings and Precautions)

Hyperkalaemia: see Warnings and Precautions

Creatinine and BUN: Increases in blood urea and plasma creatinine (1.25 times the normal considered value) were observed in both cases in 2% of patients treated with quinapril as monotherapy

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

Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.
Treatment is symptomatic and supportive consistent with established level of care.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Quinapril is rapidly de-esterified to quinaprilat (quinapril diacid, the principal metabolite) which is a potent angiotensin-converting enzyme (ACE) inhibitor (ATC Code: C09AA06).

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 10-40mg of quinapril to patients with mild to severe hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate.

Antihypertensive activity commences within one hour with peak effects usually achieved by two to four hours after dosing. Achievement of maximum blood pressure lowering effects may require two weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained in most patients throughout the 24-hour dosing interval and continue during long term therapy.

5.2 PHARMACOKINETIC PROPERTIES
Peak plasma Quinapril concentrations are observed within 1 hour of oral administration. The extent of absorption is approximately 60%, and is not influenced by food. Following absorption, Quinapril is de-esterified to its major active metabolite, quinaprilat, and to minor inactive metabolites.

Quinapril has an apparent half-life of approximately one hour. Peak plasma quinaprilat concentrations are observed approximately 2 hours following an oral dose of quinapril. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of 3 hours. In patients with renal insufficiency and creatinine clearance of ≤ 40 ml/min, peak and trough quinaprilat concentrations increase, time to peak concentration increases, apparent half-life increases, and time to steady state may be delayed. The elimination of quinaprilat is also reduced in elderly patients (≥ 65 years) and correlates well with the impaired renal function which frequently occurs in the elderly.

Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

5.3 PRECLINICAL SAFETY DATA
The results of the preclinical tests do not add anything of further significance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Magnesium carbonate, Heavy
Crospovidone
Magnesium stearate
Hydroxypropylcellulose

Coating:
Poly(ethyl acrylate, methyl methacrylate)
Macrogol 6000
Titanium dioxide (E-171)
Talc

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years
6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.
Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Quinapril 10mg Tablets are supplied in a pack of 28 tablets.
Aluminium/Aluminium-Polyamide-PVC blister strip.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special instructions needed.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way,
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0152

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/09/2009

10 DATE OF REVISION OF THE TEXT
29/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Quinapril 20 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains quinapril hydrochloride equivalent to 20mg quinapril.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Yellow, round, biconvex, with one line dividing it in half.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
• Hypertension
For the treatment of all grades of essential hypertension. Quinapril 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 should always be initiated under close medical supervision.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For oral use
Adult:
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.
Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.

Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of 2.5 mg of Quinapril is recommended in patients who are being treated with a diuretic. After this the dosage of Quinapril 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 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 furosemide) or on multiple diuretic therapy, have hypovolaemia, hyponatraemia (serum sodium < 130 mgEq/l) or systolic blood pressure < 90 mm Hg, are on high dose vasodilator therapy, have a serum creatinine > 150 µ mol/l or are aged 70 years or over.

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

Children
(6- 12 years)
Not recommended. Safety and efficacy in children have not been established
4.3 CONTRAINDICATIONS
- Quinapril is contraindicated in patients with hypersensitivity to any of the ingredients.
- Quinapril is contraindicated throughout pregnancy (see section 4.6).
- Quinapril is contraindicated in nursing mothers.
- Quinapril is contraindicated in patients with a history of angioedema related to previous treatment with ACE inhibitors.
- Quinapril is contraindicated in patients with hereditary/idiopathic angioneurotic oedema.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Quinapril 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.

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.

Hypotension:
Symptomatic hypotension was rarely seen in hypertensive patients treated with quinapril 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 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. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Quinapril. If discontinuation of the diuretic is not possible, medical supervision should be provided for up to two hours following administration of the initial dose.

Agents increasing serum potassium: Concomitant treatments with potassium sparing diuretics, potassium supplements or potassium salts should be used with caution and with appropriate monitoring of serum potassium. As with other ACE inhibitors, patients 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 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 procaaminamide: Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia. Alcohol, barbiturates or narcotics: Potentiation of orthostatic hypotension may occur

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

Antacids: May decrease the bioavailability of Quinapril

Antidiabetic drugs (oral hypoglycaemic agents and insulin): Dosage adjustments of the antidiabetic drug may be required
4.6 PREGNANCY AND LACTATION

Pregnancy: Quinapril is contraindicated throughout pregnancy. Quinapril has been shown to be foetotoxic in rabbits. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the foetus, limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios.

Should a woman become pregnant while receiving Quinapril, the drug should be discontinued as soon as possible. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If oliguria occurs, attention should be directed towards support of blood pressure and renal perfusion.

Lactation: Quinapril should not be used in nursing mothers.

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 most frequent adverse reactions in controlled clinical assays were: headache (7.2%), dizziness (5.5%), rhinitis (3.2%), coughing (3.9%), fatigue (3.5%), nausea or vomiting (2.8%) and myalgia (2.2%). Coughing is not productive, persistent and it is solved after discontinuing the treatment. The discontinuation of the treatment due to adverse reactions was only necessary in 5.2% of the patients treated with quinapril in controlled clinical assays.

Other adverse reactions present in more than 1% in patients treated with quinapril, with or without diuretics in controlled clinical assays were: diarrhoea (2.0%), chest pain (2.0%), upper respiratory tract infection (2.0%), abdominal pain (1.9%), viral infection (1.8%), dyspepsia (1.6%), dyspnoea (1.5%), back pain (1.4%), asthenia (1.3%), pharyngitis (1.3%), insomnia (1.3%), hypotension (1.1%), sinusitis (1.1%), paraesthesia (1.1%) and bronchitis (1.0%).

Reasonable, possible or definitive related or uncertain related adverse reactions with a frequency between 0.5% and 1% (except those mentioned above) in patients treated with quinapril (with or without diuretics) in controlled and uncontrolled clinical assays and in less frequent adverse events observed in clinical assays or post-commercialization experience were the following:

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

Gastro-intestinal: Flatulence, dry mouth, pancreatitis.

Nervous psychiatric: Somnolence, dizziness, depression, nervousness.

Skin: Pruritus, rash, epidermic necrolysis, alopecia, urticaria.

Urogenital: Impotence, urinary tract infections.

Others: Oedema, arthralgia, amblyopia, anaemia.

Rare reactions (<0.5%): angioedema was described in 0.1% of cases (see Warnings and Precautions and Contra-indications). Even though cases of eosinophilic pneumonitis, hepatitis or hepatic failure have been reported with the use of other ACE inhibitors, in the case of quinapril these pathologies have been very infrequent.

Laboratory finds: Seldom agranulocytosis and neutropenia have been described uncertainly related to the use of quinapril (see Warnings and Precautions)

Hyperkalaemia: see Warnings and Precautions

Creatinine and BUN: Increases in blood urea and plasma creatinine (1.25 times the normal considered value) were observed in both cases in 2% of patients treated with quinapril as monotherapy.
4.9 OVERDOSE
No data are available with respect to overdosage in humans. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion. Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. Treatment is symptomatic and supportive consistent with established level of care.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Quinapril is rapidly de-esterified to quinaprilat (quinapril diacid, the principal metabolite) which is a potent angiotensin-converting enzyme (ACE) inhibitor (ATC Code: C09AA06).

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 10–40mg of quinapril to patients with mild to severe hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate.

Antihypertensive activity commences within one hour with peak effects usually achieved by two to four hours after dosing. Achievement of maximum blood pressure lowering effects may require two weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained in most patients throughout the 24-hour dosing interval and continue during long term therapy.

5.2 PHARMACOKINETIC PROPERTIES
Peak plasma Quinapril concentrations are observed within 1 hour of oral administration. The extent of absorption is approximately 60%, and is not influenced by food. Following absorption, Quinapril is de-esterified to its major active metabolite, quinaprilat, and to minor inactive metabolites.

Quinapril has an apparent half-life of approximately one hour. Peak plasma quinaprilat concentrations are observed approximately 2 hours following an oral dose of quinapril. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of 3 hours. In patients with renal insufficiency and creatinine clearance of ≤ 40 ml/min, peak and trough quinaprilat concentrations increase, time to peak concentration increases, apparent half-life increases, and time to steady state may be delayed. The elimination of quinaprilat is also reduced in elderly patients (≥ 65 years) and correlates well with the impaired renal function which frequently occurs in the elderly.

Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

5.3 PRECLINICAL SAFETY DATA
The results of the preclinical tests do not add anything of further significance to the prescriber.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Magnesium carbonate, Heavy Crospovidone
Magnesium stearate
Hydroxypropylcellulose

Coating:
Poly (ethyl acrylate, methyl methacrylate)
Macrogol 6000
Yellow iron oxide (E-172)
Titanium dioxide (E-171)
6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.
Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER
Quinapril 20mg Tablets are supplied in a pack of 28 tablets.
Aluminium/Aluminium-Polyamide-PVC blister strip.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special instructions needed.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way,
Stevenage
Hertfordshire,
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0153

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/09/2009

10 DATE OF REVISION OF THE TEXT
29/09/2009
1 NAME OF THE MEDICINAL PRODUCT
Quinapril 40 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains quinapril hydrochloride equivalent to 40 mg quinapril.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Red, round and biconvex.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
• **Hypertension**
  For the treatment of all grades of essential hypertension. Quinapril 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 should always be initiated under close medical supervision.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For oral use

**Adult:**

**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.
Take either with or without food. The dose should always be taken at about the same time of day to help increase compliance.

Concomitant Diuretics: In order to determine if excess hypotension will occur, an initial dosage of 2.5 mg of Quinapril is recommended in patients who are being treated with a diuretic. After this the dosage of Quinapril 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 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 furosemide) or on multiple diuretic therapy, have hypovolaemia, hyponatraemia (serum sodium < 130 mgEq/l) or systolic blood pressure < 90 mm Hg, are on high dose vasodilator therapy, have a serum creatinine > 150 µ mol/l or are aged 70 years or over.

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

**Children**
(6-12 years)
Not recommended. Safety and efficacy in children have not been established
4.3 CONTRAINDICATIONS

- Quinapril is contraindicated in patients with hypersensitivity to any of the ingredients.
- Quinapril is contraindicated throughout pregnancy (see section 4.6),
- Quinapril is contraindicated in nursing mothers.
- Quinapril is contraindicated in patients with a history of angioedema related to previous treatment with ACE inhibitors.
- Quinapril is contraindicated in patients with hereditary/idiopathic angioneurotic oedema.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Quinapril 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.

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.

Hypotension:
Symptomatic hypotension was rarely seen in hypertensive patients treated with quinapril 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 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. This hypotensive effect may be effectively minimised by either discontinuing the diuretic or increasing the salt intake prior to the initial dose of Quinapril. If discontinuation of the diuretic is not possible, medical supervision should be provided for up to two hours following administration of the initial dose.

Agents increasing serum potassium: Concomitant treatments with potassium sparing diuretics, potassium supplements or potassium salts should be used with caution and with appropriate monitoring of serum potassium. As with other ACE inhibitors, patients 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 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 procarbazine: Concomitant administration with ACE inhibitors may lead to an increased risk for leucopenia. Alcohol, barbiturates or narcotics: Potentiation of orthostatic hypotension may occur

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

Antacids: May decrease the bioavailability of Quinapril

Antidiabetic drugs (oral hypoglycaemic agents and insulin): Dosage adjustments of the antidiabetic drug may be required
4.6 PREGNANCY AND LACTATION

Pregnancy: Quinapril is contraindicated throughout pregnancy. Quinapril has been shown to be foetotoxic in rabbits. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the foetus, limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios.

Should a woman become pregnant while receiving Quinapril, the drug should be discontinued as soon as possible. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If oliguria occurs, attention should be directed towards support of blood pressure and renal perfusion.

Lactation: Quinapril should not be used in nursing mothers.

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 most frequent adverse reactions in controlled clinical assays were: headache (7.2%), dizziness (5.5%), rhinitis (3.2%), coughing (3.9%), fatigue (3.5%), nausea or vomiting (2.8%) and myalgia (2.2%). Coughing is not productive, persistent and it is solved after discontinuing the treatment. The discontinuation of the treatment due to adverse reactions was only necessary in 5.2% of the patients treated with quinapril in controlled clinical assays.

Other adverse reactions present in more than 1% in patients treated with quinapril, with or without diuretics in controlled clinical assays were: diarrhoea (2.0%), chest pain (2.0%), upper respiratory tract infection (2.0%), abdominal pain (1.9%), viral infection (1.8%), dyspepsia (1.6%), dyspnoea (1.5%), back pain (1.4%), asthenia (1.3%), pharyngitis (1.3%), insomnia (1.3%), hypotension (1.1%), sinusitis (1.1%), paraesthesia (1.1%) and bronchitis (1.0%).

Reasonable, possible or definitive related or uncertain related adverse reactions with a frequency between 0.5% and 1% (except those mentioned above) in patients treated with quinapril (with or without diuretics) in controlled and uncontrolled clinical assays and in less frequent adverse events observed in clinical assays or post-commercialization experience were the following:

**Cardiovascular:** Palpitations, tachycardia, syncope, myocardial infarction, transient ischaemic attacks, cerebral haemorrhage.

**Gastro-intestinal:** Flatulence, dry mouth, pancreatitis.

**Nervous/Psychiatric:** Somnolence, dizziness, depression, nervousness.

**Skin:** Pruritus, rash, epidermic necrolysis, alopecia, urticaria.

**Urogenital:** Impotence, urinary tract infections.

**Others:** Oedema, arthralgia, amblyopia, anaemia.

Rare reactions (<0.5%): angioedema was described in 0.1% of cases (see Warnings and Precautions and Contra-indications). Even though cases of eosinophilic pneumonitis, hepatitis or hepatic failure have been reported with the use of other ACE inhibitors, in the case of quinapril these pathologies have been very infrequent.

Laboratory finds: Seldom agranulocytosis and neutropenia have been described uncertainly related to the use of quinapril (see Warnings and Precautions)

**Hyperkalaemia:** see Warnings and Precautions

**Creatinine and BUN:** Increases in blood urea and plasma creatinine (1.25 times the normal considered value) were observed in both cases in 2% of patients treated with quinapril as monotherapy.
4.9 OVERDOSE
No data are available with respect to overdosage in humans. The most likely clinical manifestation would be symptoms attributable to severe hypotension, which should normally be treated by intravenous volume expansion. Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat. Treatment is symptomatic and supportive consistent with established level of care.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Quinapril is rapidly de-esterified to quinaprilat (quinapril diacid, the principal metabolite) which is a potent angiotensin-converting enzyme (ACE) inhibitor (ATC Code: C09AA06).

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 10-40mg of quinapril to patients with mild to severe hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate.

Antihypertensive activity commences within one hour with peak effects usually achieved by two to four hours after dosing. Achievement of maximum blood pressure lowering effects may require two weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained in most patients throughout the 24-hour dosing interval and continue during long term therapy.

5.2 PHARMACOKINETIC PROPERTIES
Peak plasma Quinapril concentrations are observed within 1 hour of oral administration. The extent of absorption is approximately 60%, and is not influenced by food. Following absorption, Quinapril is de-esterified to its major active metabolite, quinaprilat, and to minor inactive metabolites.

Quinapril has an apparent half-life of approximately one hour. Peak plasma quinaprilat concentrations are observed approximately 2 hours following an oral dose of quinapril. Quinaprilat is eliminated primarily by renal excretion and has an effective accumulation half-life of 3 hours. In patients with renal insufficiency and creatinine clearance of ≤ 40 ml/min, peak and trough quinaprilat concentrations increase, time to peak concentration increases, apparent half-life increases, and time to steady state may be delayed. The elimination of quinaprilat is also reduced in elderly patients (> 65 years) and correlates well with the impaired renal function which frequently occurs in the elderly.

Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired de-esterification of quinapril. Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

5.3 PRECLINICAL SAFETY DATA
The results of the preclinical tests do not add anything of further significance to the prescriber.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Magnesium carbonate, Heavy
Crospovidone
Magnesium stearate
Hydroxypropylcellulose

Coating:
Poly (ethyl acrylate, methyl methacrylate)
Macrogol 6000
Red iron oxide (E-172)
Titanium dioxide (E-171)
INCOMPATIBILITIES
Not applicable.

SHELF LIFE
3 years

SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.
Store in the original package.

NATURE AND CONTENTS OF CONTAINER
Quinapril 40mg Tablets are supplied in a pack of 28 tablets.
Aluminium/Aluminium-Polyamide-PVC blister strip.

SPECIAL PRECAUTIONS FOR DISPOSAL
No special instructions needed.

MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way,
Stevenage
Hertfordshire,
SG1 4SZ
United Kingdom

MARKETING AUTHORISATION NUMBER(S)
PL 18909/0154

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/09/2009

DATE OF REVISION OF THE TEXT
29/09/2009
UKPAR Quinapril 5mg, 10mg, 20mg and 40mg Tablets

PATIENT INFORMATION LEAFLET

QUINAPRIL 5 mg TABLETS
QUINAPRIL 10 mg TABLETS
QUINAPRIL 20 mg TABLETS
QUINAPRIL 40 mg TABLETS

Read all of this leaflet carefully before you start taking this medicine. It provides important information on your medicine. Keep the leaflet until you have finished this medicine. You may need to read it again. If you have any further questions or are not sure about anything, please ask your doctor or your pharmacist.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them even if their symptoms are the same as yours.

In this leaflet:
1. What is in this medicine?
2. Who has made this medicine?
3. What Quinapril Tablets are and what they are used for
4. Before you take your medicine
5. How to take your medicine
6. Possible side effects
7. Storing Quinapril Tablets

1. WHAT IS IN THIS MEDICINE?

Quinapril Tablets come in four different strengths and are round yellow (5mg), white (10mg), yellow (20mg) and red (40mg) coated tablets. Quinapril 5mg, 10mg and 20mg tablets have a centre break line on one side.

Each tablet contains 5, 10, 20 or 40mg of the active ingredient quinapril.

Quinapril 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.

4. BEFORE YOU TAKE THIS MEDICINE

Make sure it is safe for you to take quinapril. If the answer to any of the questions below is yes, do not take this medicine and consult your doctor or pharmacist for advice.

Quinapril may not be suitable for you.

- Have you ever had an allergic reaction to quinapril or to other similar medicines (any other ACE inhibitor) or to any of the other ingredients in this medicine? An allergic reaction may cause symptoms such as rash, itching, swollen lips or face, or difficulty breathing.
- Are you pregnant, trying to become pregnant, or breast feeding? Quinapril must not be taken by pregnant women as it
These tablets also contain the inactive ingredients: Magnesium Carbonate Heavy, Hydroxypropylcellulose, Crospovidone, Magnesium Stearate, Poly(ethyl acrylate, methyl methacrylate), Titanium Dioxide (E-171), Talc and Macrogol.

The 5mg, 20mg and 40mg strengths also contain iron oxides as colours.

Quinapril Tablets is supplied in blister packs of 28 tablets.

Your doctor may have given you this medicine before from another company and it may have looked slightly different. Either brand will have the same effect.

2. WHO HAS MADE THIS MEDICINE?

This medicine is manufactured by Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, United Kingdom, who is also the Marketing Authorisation holder.

3. WHAT IS THIS MEDICINE USED FOR?

Quinapril is an ACE inhibitor used to treat high blood pressure, so called hypertension, and to help treat heart failure. Quinapril is used for the treatment of all grades of essential hypertension. Quinapril is effective as monotherapy (i.e. alone) or together with diuretics in persons with hypertension. Quinapril can also be used for the treatment of heart failure when given together with a diuretic and/or cardiac glycoside.

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

There may affect the unborn baby.

- Are you taking diuretics (water tablets) as well as Quinapril Tablets? If so then talk to your doctor before taking these tablets, if you have not already done so, as he may want to observe you when you take your first dose.

If the answer to any of the following questions is yes, special caution may be necessary and you should tell your doctor or pharmacist:

- Do you have any problems with your liver, kidney or heart?
- Do you have breathing difficulties such as asthma?
- Are you breast-feeding?
- Do you have epilepsy (fits)?
- Do you have a history of bleeding disorders?
- Do you have aortic stenosis (narrowing of the main blood vessel from the heart)?
- Do you use a haemodialysis machine (an artificial kidney)?
- Do you have collagen vascular disease, which include the conditions rheumatoid arthritis, systemic lupus erythematosus and scleroderma?
- Are you having, or about to have, low density lipoprotein apheresis treatment (removal of cholesterol from your blood by machine)?
- Are you having, or about to have, desensitisation treatment, i.e. to reduce the effects of an allergy to a bee or wasp sting?

If you go into hospital or visit a dentist, remember to tell them that you are taking quinapril. This is important if you go into hospital for an operation as your anaesthetist will want to know.
Are you taking any other medicines?
Some medicines may not work well with quinapril or might react badly. You must make sure that your doctor is aware of all other medicines that you are taking, or have recently taken, even medicines or remedies you have bought for yourself without a prescription. In particular you should check with your doctor or pharmacist before taking quinapril together with any of the following medicines:
- Tetracycline – an antibiotic
- Blood pressure lowering medicines (captopril, enalapril, lisinopril)
- Antacids – medicines to treat heart burn or indigestion
- Antidiabetic drugs (oral agents e.g. glibenclamide, metformin and insulin)
- Non-steroidal anti-inflammatory drugs e.g. aspirin or ibuprofen
- Lithium supplements used for certain mental illness
- Potassium supplements
- Diuretics (Water tablets)
- Anaesthetic agents used in surgery
- Steroids (hydrocortisone, dexamethasone or prednisolone)
- ACTH (tetraacosactrin)
- Procainamide (for irregular heart beat), drugs to treat cancer (cytostatic drugs), drugs used after organ transplants (ciclosporines), allopurinol, sympathomimetics, indigestion/heartburn medicines or sedatives.

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

If you see another doctor or dentist, or visit a hospital, remember to tell them what medicines you are already taking.

6. POSSIBLE SIDE EFFECTS
Quinapril can sometimes cause side-effects. These might be:
- Neutropenia/agranulocytosis (a lack of certain white blood cells which may lead to infection, sore throat or fever). Tell your doctor at once if you get these symptoms. This reaction is more likely if you have collagen vascular disease which include the conditions rheumatoid arthritis, systemic lupus erythematosus and scleroderma. If you have collagen vascular disease your doctor may perform routine tests to check your blood.
- Hypotension (low blood pressure). This is more likely to occur if you have been taking diuretics (water tablets), have been drinking alcohol or you are dehydrated or on dialysis. If you get low blood pressure you may feel light headed or faint. Lie down until this feeling passes and tell your doctor at once.
- Angioedema (swelling of the face, tongue and windpipe which can cause great difficulty in breathing). This is a very rare reaction, but it can be serious if it occurs. You should tell your doctor at once if it happens.

Other side effects sometimes seen are:
- Dry mouth, taste disturbances, nausea or vomiting (feeling or being sick), diarrhea, upset stomach, stomach pain or wind, constipation, jaundice.
- Headache, dizziness, confusion, nervousness, insomnia (being unable to sleep), blurred vision, ringing in the ears, feeling tired or run down, general feeling of weakness, depression.
- Coughing, sneezing, runny nose, sore throat, sinusitis (inflammation of the sinuses) or upper respiratory tract infection. Bronchitis or viral infections.
- Pain in the chest, muscles or joints.
Pregnancy and Breast-feeding
Quinapril should not be used during pregnancy and should not be used by nursing mothers.

Driving and using machines
Although quinapril is unlikely to affect your ability to drive, it may vary occasionally cause sleepiness, dizziness, or light-headedness. Do not drive or operate machinery if you are affected.

5. HOW TO TAKE QUINAPRIL TABLETS
Quinapril Tablets are usually taken once or twice a day. You will start on a low dose which may be increased if necessary by your doctor until you are taking exactly the amount you need.

For hypertension (high blood pressure) the starting dose is usually 10mg, which may be increased to 20 to 40mg a day.

For heart failure, or hypertension in combination with a diuretic, the starting dose is usually 2.5mg, which may be increased up to 10 to 40mg a day. Occasionally, some people need higher doses than this. Whatever dose you have been prescribed, follow your doctor’s instructions exactly and never change the dose yourself.

Swallow the tablets whole with a drink of water. Do not chew them.

Quinapril is not recommended for children under the age of 12 years, as there is not yet sufficient experience with this medicine in children.

It is best to take your tablets approximately the same time each day. It will also help you remember to take the tablets.

If you take more Quinapril Tablets than you should:
It is important not to take too many tablets as this may be dangerous. If you or someone else has taken more tablets than you should, or if you think a child has swallowed any, contact your doctor or hospital accident and emergency department immediately. Take this leaflet, and any tablets that you still have to show the doctor.

If you forget to take your medicine:
If you forget to take your usual dose at the right time, take it as soon as you remember. Do not take two doses together to make up for the forgotten dose. If it is nearly time to take the next dose, wait until then and then carry on as before.

Although an occasional missed dose is not likely to cause problems, you should tell your doctor if you often miss a dose because of difficulty in remembering, as your treatment may not be fully effective.

- Skin rash, itch or paraesthesia (pins and needles). Severe skin rash associated with general illness. Increased sensitivity to sunlight. Hair loss.
- Palpitations (pounding heart), increased heart rate, oedema (swelling of the ankles), impotence (reduced sexual function).
- Pancreatitis (inflammation of the pancreas), kidney disease (your doctor may carry out tests at times during your treatment if he thinks you may be at risk from kidney disease).
- Hyperkalaemia (having too much potassium in your blood).
- Hepatitis (inflammation of the liver).

If you get any of these, or any other unusual effects, tell your doctor or pharmacist at once.

If you experience any dizzy spells you should avoid driving or operating machinery.

Quinapril Tablets may cause certain changes in your blood and your doctor may do blood tests to monitor this. The following changes have occurred in some patients taking these tablets or other similar medicines.
- An increase in creatinine or blood urea nitrogen (substances which can tell how well your kidneys are working).
- An increase in liver enzymes and serum bilirubin (substances which can tell how well your liver is working).
- A decrease in the number of platelets, which may affect blood clotting. If you notice unexplained bruising or red/purple spots on the skin you should see your doctor.
- Decreases in red and white blood cells.

7. STORING QUINAPRIL TABLETS
Do not use this medicine after the exp. date on the carton.

Keep the tablets in a dry place at normal room temperature (below 25°C) in the packaging they come in.

You should return any out-of-date tablets to your pharmacist for safe disposal.

KEEP ALL MEDICINES OUT OF THE REACH AND SIGHT OF CHILDREN.

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Quinapril 5mg Tablets
28 Film-coated tablets

Each film-coated tablet contains Quinapril hydrochloride equivalent to 5mg quinapril