

PRODUCT INFORMATION

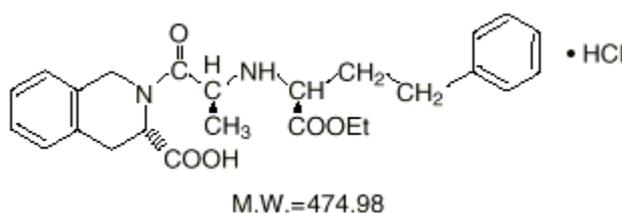
AQUINAFIL[®] (quinapril hydrochloride)

NAME OF THE MEDICINE

AQUINAFIL (quinapril hydrochloride) 5 mg, 10 mg and 20 mg tablets.

AQUINAFIL contains the active ingredient quinapril hydrochloride. Quinapril hydrochloride is the hydrochloride salt of quinapril, the ethyl ester of a nonsulfhydryl, angiotensin-converting enzyme (ACE) inhibitor, quinaprilat. Quinapril is chemically and pharmacologically related to enalapril.

The structural formula of quinapril hydrochloride is shown below:



Chemical name:	2-(S)-[N-[[1-ethoxycarbonyl]-3-phenylpropyl]- (S)-alanyl]-1,2,3,4-tetrahydro-3-(S)-isoquinoline carboxylic acid, monohydrochloride
Molecular formula:	C ₂₅ H ₃₀ N ₂ O ₅ .HCl
Molecular weight:	474.98
CAS Registry Number:	82586-55-8.

DESCRIPTION

Quinapril hydrochloride is a white to off-white amorphous powder that is freely soluble in aqueous solvents. The drug molecule contains three chiral centres but is present as the pure S-S-S-stereoisomer.

AQUINAFIL tablets also contain magnesium carbonate hydrate,, lactose monohydrate, gelatin, crospovidone, magnesium stearate, candelilla wax and Opadry Y-5-0920.

PHARMACOLOGY

Pharmacodynamics

Quinapril is deesterified to the principal metabolite, quinaprilat, which is an inhibitor of ACE activity in human subjects and animals. ACE is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the vasoconstrictor, angiotensin II. The effect of quinapril in

hypertension appears to result primarily from the inhibition of circulating and tissue ACE activity, thereby reducing angiotensin II formation. Quinapril inhibits the elevation in blood pressure caused by intravenously administered angiotensin I, but has no effect on the pressor response to angiotensin II, noradrenaline or adrenaline. Angiotensin II also stimulates the secretion of aldosterone from the adrenal cortex, thereby facilitating renal sodium and fluid reabsorption. Reduced aldosterone secretion by quinapril may result in a small increase in serum potassium. In controlled hypertension trials, treatment with quinapril alone resulted in mean increases in potassium of 0.07 mmol/L (see **PRECAUTIONS**). Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA).

Quinapril has been shown to be effective in the treatment of congestive heart failure and hypertension. While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, quinapril exerts antihypertensive actions even in patients with low renin hypertension. Quinapril was an effective antihypertensive in all races studied, although it was somewhat less effective in black patients (usually a predominantly low renin group) than in non-black patients. ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator. Bradykinin acts on bradykinin receptors in the vascular endothelium to promote the release of the vasodilators such as nitric oxide and prostacyclin. Whether increased levels of bradykinin play a role in the therapeutic effect of quinapril remains to be elucidated.

ACE inhibitors, including quinapril, may enhance insulin sensitivity.

Endothelial Dysfunction

Endothelial dysfunction is associated with hypertension and heart failure and is considered an important pathophysiological mechanism in cardiovascular disease. Quinapril has been shown to improve endothelium-dependent vasomotor function by mechanisms leading to increased availability of nitric oxide. The clinical significance of improving endothelial function has not yet been established.

In patients with chronic heart failure (NYHA function class III) (n=40), intra-arterial infusion of quinaprilat 1.6 µg/min (n=15) significantly increased endothelium mediated flow-dependent dilation (FDD) in the radial artery by >40% (change in FDD: quinapril=10.2±0.6% versus control=6.9±0.6%; p<0.01). In a six month placebo-controlled trial (n=105), normotensive patients, with and without a history of hypertension, who were free of left ventricular dysfunction and severe dyslipidaemia and who required percutaneous coronary artery revascularisation, were treated with quinapril 40 mg daily (n=51). There was an endothelium-dependent reduction of acetylcholine-induced intra-arterial vasoconstriction of the coronary arteries (4.5±3.0% and 12.1±3.0% at 10⁻⁶ and 10⁻⁴ mol/L respectively; overall p=0.002) (TREND study). Flow-mediated vasodilation (FMD) of the brachial artery was significantly increased to 9.1% from a baseline of 7.3% (change in FMD: 1.8 ± 1.0%; p<0.02) in patients with coronary artery disease treated with quinapril 20 mg daily (n=56) for 8 weeks in a partial-block, cross-over, blinded study of 80 patients comparing the effect of four anti-hypertensives on brachial flow-mediated vasodilation (BANFF study).

Clinical Effects

Single doses of 20 mg of quinapril provide over 80% inhibition of plasma ACE for 24 hours. Inhibition of the pressor response to angiotensin I is shorter-lived, with a 20 mg dose giving

75% inhibition for about 4 hours, 50% inhibition for about 8 hours, and 20% inhibition at 24 hours. With chronic dosing, however, there is substantial inhibition of angiotensin II levels at 24 hours by doses of 20 to 80 mg.

Hypertension

Administration of 10 to 40 mg quinapril to patients with essential hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate. Antihypertensive activity commences within 1 hour with peak effects usually achieved by 2 to 4 hours after dosing. Achievement of maximum blood pressure lowering effects may require 2 weeks of therapy in some patients. At the recommended doses, antihypertensive effects are maintained throughout the 24 hour dosing interval and continue during long-term therapy with no evidence of tolerance.

Haemodynamic assessments in patients with hypertension indicate that blood pressure reduction produced by quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate, cardiac index, renal blood flow, glomerular filtration rate, or filtration fraction.

Use of quinapril with a thiazide diuretic gives a blood-pressure lowering effect greater than that seen with either agent alone.

In patients with hypertension, quinapril 10 to 40 mg was similar in effectiveness to captopril, enalapril, propranolol, and thiazide diuretics.

Therapeutic effects appear to be the same for elderly (≥ 65 years of age) and younger adult patients given the same daily dosages, with no increase in adverse events in elderly patients.

Heart Failure

When compared with placebo therapy, quinapril administration to patients with congestive heart failure in most controlled studies has prolonged exercise time only modestly, or not at all. On the other hand, the cessation of quinapril therapy in patients stabilised on this therapy together with diuretic therapy has been shown to result in progressive clinical deterioration in the control of heart failure. While some short-term placebo controlled studies have demonstrated significant improvements in NYHA functional class with quinapril therapy, other studies have not. In longer term but controlled studies, more consistent improvements in NYHA functional class with quinapril therapy have been demonstrated. There is a lack of data to support an improved prognosis in congestive heart failure. The effects of quinapril on long-term mortality in heart failure have not been evaluated.

Pharmacokinetics

The pharmacokinetics of quinapril and quinaprilat are linear over a single-dose range of 5 to 80 mg doses and 40 to 160 mg in multiple daily doses.

Absorption

Following oral administration, peak plasma quinapril concentrations are observed within 1 hour. Based on recovery of quinapril and its metabolites in urine, the extent of absorption is at least 60%. The rate and extent of quinapril absorption are diminished moderately

(approximately 25 to 30%) when quinapril hydrochloride tablets are administered during a high-fat meal.

Distribution

Approximately 97% of either quinapril or quinaprilat circulating in plasma is bound to proteins.

Metabolism

Following absorption, quinapril is deesterified to its major active metabolite, quinaprilat (about 38% of oral dose), and to other minor inactive metabolites. Following multiple oral dosing of quinapril, there is an effective accumulation half-life of quinaprilat of approximately 3 hours, and peak plasma quinaprilat concentrations are observed approximately 2 hours post-dose.

Elimination

Quinaprilat is eliminated primarily by renal excretion, up to 96% of an IV dose. It has an apparent elimination half-life in plasma of approximately 2 hours representing the clearance of the free quinaprilat from the plasma and a prolonged terminal phase with a half-life of 25 hours thought to reflect the slow release of quinaprilat from ACE.

Special Populations

Renal Impairment

In patients with renal insufficiency, the elimination half-life of quinaprilat increases as creatinine clearance decreases. There is a linear correlation between plasma quinaprilat clearance and creatinine clearance. In patients with end-stage renal disease, chronic haemodialysis or continuous ambulatory peritoneal dialysis has little effect on the elimination of quinapril and quinaprilat. A study in 20 patients with renal impairment (creatinine clearance 12 to 119 mL/min/1.73 m²) showed alterations in both quinapril and quinaprilat pharmacokinetics. The C_{max} and AUC for quinapril were greater in patients with renal impairment and the elimination half-life tended to be longer. However, these changes were small and probably not clinically important. The pharmacokinetic data for quinaprilat were markedly different. C_{max}, AUC and the elimination half-life all increased as renal impairment became greater. When the creatinine clearance was below 40 mL/min/1.73 m², trough levels of quinaprilat were markedly increased. The elimination half-life increased from 2 to 4 hours as creatinine clearance fell from 120 to 40 mL/min/1.73 m² and increased further to 12 to 14 hours when creatinine was 12 mL/min/1.73 m². Thus, if a person has a creatinine clearance below 40 mL/min/1.73 m², then it is likely that quinaprilat will accumulate and quinapril therapy should be started at a low dose and gradually titrated upward. If creatinine clearance is greater than 40 mL/min/1.73 m², quinapril and quinaprilat are unlikely to accumulate (see **PRECAUTIONS, Impaired Renal Function** and **DOSAGE AND ADMINISTRATION, Use in Renal Impairment**).

Hepatic Impairment

The elimination half-life of quinapril was found to have doubled in patients with hepatic impairment from alcoholic cirrhosis when compared to age-matched healthy volunteers. This indicates that liver metabolism is an important facet of quinapril metabolism. There was no

alteration in the elimination half-life of quinaprilat probably because renal excretion is its principal route of elimination. The plasma quinaprilat levels, were, however, lower than in matched controls. These results suggested that not only the rate but the extent of the conversion of quinapril to quinaprilat was impaired. Particularly in patients with severe hepatic insufficiency there may be a reduction in efficacy of quinapril due to failure of conversion to the active metabolite. Quinaprilat concentrations are reduced in patients with alcoholic cirrhosis due to impaired deesterification of quinapril (see **PRECAUTIONS, Impaired Hepatic Function**).

Cardiac Impairment

The presence of mild to moderate congestive heart failure *per se* appears to have minimal effect on the pharmacokinetics of quinaprilat, except in so far that congestive heart failure may be associated with renal failure. Dosing of quinapril in patients with congestive heart failure should be based on their renal function.

Elderly (≥65 years)

Elimination of quinaprilat is reduced in elderly patients (≥65 years); this reduction is attributable to a decrease in renal function (see **PRECAUTIONS, Use in the Elderly** and **DOSAGE AND ADMINISTRATION, Use in the Elderly**) and not to age itself.

Studies in rats indicate that quinapril and its metabolites do not cross the blood-brain barrier.

INDICATIONS

Hypertension

AQUINAFIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics. Sufficient data have not been provided to support the use of AQUINAFIL in renovascular hypertension.

Congestive Heart Failure

AQUINAFIL is indicated as an adjunctive treatment of mild to moderate congestive heart failure when given concomitantly with a diuretic and/or cardiac glycoside.

CONTRAINDICATIONS

AQUINAFIL is contraindicated in:

- Patients who are hypersensitive to quinapril or any of the other ingredients in the tablet.
- Patients with a history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an ACE inhibitor.
- Combination with sacubitril/valsartan due to the increased risk of angioedema.

- Severe renal artery stenosis.
- Patients haemodialysed using high-flux polyacrylonitrile ('AN69') membranes (see **PRECAUTIONS, Anaphylactoid Reactions During Haemodialysis**).
- Pregnancy (see **PRECAUTIONS, Use in Pregnancy**). Women who intend to become pregnant, or of childbearing potential, unless on an effective contraceptive and highly unlikely to conceive.

Do not administer AQUINAFIL in combination with aliskiren in:

- Patients with diabetes.
- Patients with moderate to severe kidney insufficiency (GFR <60 mL/min/1.73 m²).
- Patients with hyperkalaemia (>5 mmol/L).
- Congestive heart failure patients who are hypotensive.

Do not administer AQUINAFIL in combination with angiotensin receptor blockers or other ACE inhibitors in:

- Diabetic patients with end organ damage.
- Patients with moderate to severe kidney insufficiency (GFR <60 mL/min/1.73 m²).
- Patients with hyperkalaemia (>5 mmol/L).
- Congestive heart failure patients who are hypotensive.

PRECAUTIONS

Angioedema

Since 1984, severe life-threatening angioedema has been reported with most of the ACE inhibitors. The overall incidence with some of the ACE inhibitors is approximately 0.1 to 0.2%. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually the angioedema is nonpitting oedema of the skin, mucous membrane or subcutaneous tissue.

The onset of angioedema associated with the use of ACE inhibitors may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals. Angioedema may occur with or without urticaria.

Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors. In such cases the product should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema can be fatal or near fatal. There seems to be no difference

in the incidence of angioedema in patients of either sex or in those with heart failure or hypertension. In the majority of reported cases the symptoms occurred during the first week of therapy.

In USA studies, black patients receiving ACE inhibitor monotherapy have been reported to have a higher incidence of angioedema compared to non-black patients. It should also be noted that, in controlled clinical trials conducted in Europe and North America, ACE inhibitors have an effect on blood pressure that is less in black patients than in non-black patients.

Patients taking concomitant mTOR inhibitor (e.g. temsirolimus) or concomitant DPP-IV inhibitor (e.g. vildagliptin) therapy or a neutral endopeptidase inhibitor may be at increased risk for angioedema. Caution should be used when starting an mTOR inhibitor or a DPP-IV inhibitor or a neutral endopeptidase inhibitor (see **CONTRAINDICATIONS**) in a patient already taking an ACE inhibitor.

Intestinal Angioedema

Intestinal angioedema has been reported in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there has been no prior history of facial angioedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery, and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

There are reports where switching to another ACE inhibitor was followed by recurrence of oedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angioedema to a drug of this class (see **CONTRAINDICATIONS**). Where involvement of tongue, glottis or larynx is likely to cause airway obstruction, appropriate therapy, including adrenaline and oxygen administration, should be carried out promptly or the patient hospitalised. Medical therapy of progressive angioedema should be aggressive. Failing a rapid response, oral/nasal intubation or securing an airway by surgical means (e.g. cricothyrotomy or tracheostomy) may be necessary followed by mechanical ventilation. Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

Hypotension

Hypotension may occur in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in uncomplicated hypertensive patients but is a possible consequence of use in patients with impaired renal function, in salt/volume depleted patients such as patients with renovascular hypertension, vomiting or diarrhoea, those treated vigorously with diuretics, or patients undergoing dialysis (see **INTERACTIONS WITH OTHER MEDICINES** and **ADVERSE EFFECTS**). In patients with severe congestive heart failure with or without associated renal insufficiency, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or

progressive azotaemia, but rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses under very close supervision. Such patients should be followed closely for the first 2 weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

Similar considerations may apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. In all high risk patients, it is advisable to initiate treatment at lower dosages than those usually recommended for uncomplicated patients.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Patients already receiving a diuretic when AQUINAFIL is initiated can develop symptomatic hypotension. In these patients it is important, if possible, to stop the diuretic for 2 to 3 days before starting AQUINAFIL. If blood pressure is not controlled with AQUINAFIL alone, the diuretic should be resumed. If it is not possible to withdraw diuretic therapy, begin AQUINAFIL at a low initial dose.

Anaphylactoid Reactions During Desensitisation

Patients receiving ACE inhibitors during desensitising treatment with hymenoptera venom have sustained life-threatening anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld, but they have reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During LDL Apheresis

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

Anaphylactoid Reactions During Haemodialysis

Clinical evidence has shown that patients haemodialysed using certain high-flux membranes (such as polyacrylonitrile membranes) are likely to experience anaphylactoid reactions with concomitant ACE inhibitor treatment. This combination should therefore not be used (see **CONTRAINDICATIONS**). The use of either alternative antihypertensive drugs, or alternative membranes for haemodialysis is recommended (e.g. cuprophane or polysulphone PSF).

Impaired Renal Function

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 AQUINAFIL, may be associated with oliguria

and/or progressive azotaemia and rarely acute renal failure and/or death (see **ADVERSE EFFECTS**).

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 20% of patients. These increases were usually reversible upon discontinuation of the ACE inhibitor. ACE inhibitors should not be used in patients with known or suspected renal artery stenosis (see **CONTRAINDICATIONS**). When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney or with bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II-induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

The half-life of quinaprilat is prolonged as creatinine clearance falls. Patients with a creatinine clearance of <60 mL/min require a lower initial dosage of quinapril (see **DOSAGE AND ADMINISTRATION**). These patients' dosage should be titrated upwards based upon therapeutic response, and renal function should be closely monitored although initial studies do not indicate that quinapril produces further deterioration in renal function.

In people with a creatinine clearance <40 mL/min/1.73 m², quinaprilat did accumulate but not as much as would be suggested by the increased half-life (2.2 to 12 hours), implying that alternative methods of removal become important. Some hypertensive or heart failure patients with no apparent pre-existing renovascular disease have developed increases in blood urea nitrogen and serum creatinine, which is usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required.

If deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of renal function may not be apparent from measurement of blood urea and serum creatinine.

Some ACE inhibitors have been associated with the occurrence of proteinuria (up to 0.7%) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium-sparing diuretics or high doses of other diuretics, limited cardiac reserve, or treatment with a non-steroidal anti-inflammatory drug.

Evaluation of hypertensive patients should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**).

Impaired Hepatic Function

Hepatitis or hepatic failure have been rarely seen in clinical trials with quinapril, however, hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with other ACE inhibitors in patients with or without

pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug. In patients with hepatic impairment from alcoholic cirrhosis, it has been shown that the half-life of quinapril was doubled in comparison to age-matched controlled volunteers. This indicates that liver metabolism is an important facet of quinapril metabolism. There was no alteration in the half-life of quinaprilat probably because renal excretion is its principal method of removal. The plasma quinaprilat levels were, however, lower than matched controls. The results suggested that not only the rate but also the extent of the conversion of quinapril to quinaprilat were impaired. Particularly in patients with severe hepatic insufficiency there may be a reduction in efficacy of quinapril due to failure of conversion to the active metabolite.

Quinapril when combined with a diuretic should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Fetal/Neonatal Morbidity and Mortality

See **PRECAUTIONS, Use in Pregnancy**.

Cough

Cough has been reported with the use of ACE inhibitors, including quinapril. Characteristically, the cough is persistent, dry, non-productive and resolves after discontinuation of therapy. The frequency of reports has been increasing since cough was first recognised as a side effect of ACE inhibitor therapy. In various studies, the incidence of cough varies between 2% to 15% depending on the drug, dosage and duration of use. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

The cough is often worse when lying down or at night, and has been reported more frequently in women (who account for two-thirds of the reported cases). Patients who cough may have increased bronchial reactivity compared to those who do not. The observed higher frequency of this side effect in non-smokers may be due to a higher level of tolerance in smokers to cough.

The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins which accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drug may be required in severe cases.

Hypoglycaemia and Diabetes

ACE inhibitors have been associated with hypoglycaemia in diabetic patients on insulin or oral hypoglycaemic agents; closer monitoring of diabetic patients may be required.

Hyperkalaemia

ACE inhibitors decrease the formation of angiotensin II, which results in decreased production of aldosterone and an increase in serum potassium levels (>5.5 mEq/L). Hyperkalaemia is more likely in patients with some degree of renal impairment, those taking

concomitant potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs known to raise serum potassium levels. Diabetics and elderly patients particularly, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may co-exist with hyperkalaemia. It is recommended that patients undergoing ACE inhibitor treatment should have serum electrolytes (including potassium, sodium and urea) measured from time to time (see **INTERACTIONS WITH OTHER MEDICINES**). This is more important in patients taking diuretics. When administered concomitantly, quinapril may reduce the hypokalaemia induced by thiazide diuretics.

Hyponatraemia and Syndrome of Inappropriate Anti-diuretic Hormone (SIADH)

Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatraemia has been observed in some patients treated with other ACE inhibitors. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatraemia.

Neutropenia/Agranulocytosis

Agranulocytosis and bone marrow depression (including leucopenia/neutropenia) have been reported with ACE inhibitors. These have mostly occurred in patients with pre-existing impaired renal function, collagen vascular disease, immunosuppressant therapy or a combination of these complicating factors. Most episodes of leucopenia and neutropenia have been single, transient occurrences without any associated clinical symptoms. In addition, data to establish a causal relationship are currently lacking.

It is recommended that periodic monitoring of white blood cell counts should be considered in patients with collagen vascular disease, renal disease (serum creatinine ≥ 180 $\mu\text{mol/L}$) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.

Dermatological Reactions

Dermatological reactions characterised by maculopapular pruritic rashes and sometimes photosensitivity have been reported rarely with ACE inhibitors. Rare and sometimes severe skin reactions (e.g. lichenoid eruptions, psoriasis, pemphigus-like rash, rosacea, Stevens-Johnson syndrome) have also been reported. A causal relationship is difficult to assess.

A cutaneous reaction to one ACE inhibitor may not occur with another drug of the same class. There have, however, been reports of cross-reactivity.

Taste Disturbance (Dysgeusia)

The incidence of taste disturbance was reported to be high (up to 12.5%) with high doses of one ACE inhibitor, but the overall incidence for the class is probably low ($<0.5\%$). However, the relevant data are scarce and difficult to interpret.

Taste disturbance has been described as a suppression of taste or a metallic sensation in the mouth. The dysgeusia usually occurs in the first few weeks of treatment and may disappear within 1 to 3 months despite continued treatment.

Surgery/Anaesthesia

In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater in patients receiving ACE inhibitors because of interference with compensatory mechanisms associated with the renin-angiotensin system. If perioperative hypotension occurs, volume expansion would be required.

Valvular Stenosis

Patients with aortic stenosis are at a particular risk of decreased coronary perfusion and hypotension when treated with vasodilators. Vasodilators may tend to drop diastolic pressure, and hence coronary perfusion pressure, without producing the concomitant reduction in myocardial oxygen demand that normally accompanies vasodilatation. The true clinical importance of this concern is uncertain. Nevertheless, ACE inhibitors should be avoided in such patients.

Concomitant use of ACE Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist) and an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Concomitant use of all three classes of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the treatment. The concomitant use of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

As a consequence of inhibiting the RAAS, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals with congestive heart failure, especially if combining medicinal products that affect this system. Dual blockade of the RAAS with ACE-inhibitors, angiotensin receptor blockers or a direct renin inhibitor such as aliskiren, is associated with an increased risk of developing these conditions compared to monotherapy. Routine combination therapy with RAAS acting agents is not recommended and should be limited to individually defined cases with close monitoring of blood pressure, renal function and electrolyte levels (see **CONTRAINDICATIONS**).

Use in Pregnancy

Category D.

As with all ACE inhibitors, AQUINAPRIL is contraindicated in pregnancy (see **CONTRAINDICATIONS**). Pregnancy should be excluded before starting treatment with AQUINAFIL and avoided during the treatment. If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment. When pregnancy is detected, the ACE inhibitor should be discontinued as soon as possible and arrangements for further care should be made.

Infants exposed to ACE inhibitors during pregnancy may be at an increased risk for malformations of the cardiovascular system and central nervous system. A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to any ACE inhibitor during first trimester compared with no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared with no exposure.

Post-marketing experience with all ACE inhibitors suggest that exposure *in utero* may be associated with hypotension and decreased renal perfusion in the fetus. ACE inhibitors have been associated with fetal death *in utero*. Adverse effects appear to be most likely in the second and third trimesters.

There have also been reports of prematurity, hypotension, renal system disorders (including renal failure), skull hypoplasia, oligohydramnios, limb contractures, craniofacial deformities, hypoplastic lung development, intrauterine growth retardation, patent ductus arteriosus, fetal death and/or death in the newborn in association with the maternal use of ACE inhibitors.

Infants with a history of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia. If such complications occur, attention should be directed toward support of blood pressure and renal perfusion. Haemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

Use in Lactation

ACE inhibitors, including quinapril, are secreted in human milk to a limited extent. Because of the potential for serious reactions in nursing infants, AQUINAFIL should not be given to a nursing mother.

Paediatric Use

The safety and effectiveness of AQUINAFIL in children have not been established.

Use in the Elderly

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of quinapril where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Carcinogenicity

At least one other ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential of ACE inhibitors to cause this effect in man is unknown. Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign.

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day for 104 weeks. Female rats given the highest dose level have an increased incidence of mesenteric lymph node haemangiomas and skin/subcutaneous lipomas.

Genotoxicity

Neither quinapril nor quinaprilat are mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicological studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro* chromosome aberration with V79 cultured lung cells and an *in vivo* cytogenetic study with rat bone marrow.

Effects on Fertility

There were no adverse effects on fertility or reproduction in rats at oral doses up to 100 mg/kg/day.

Effects on Ability to Drive and Use Machines

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

INTERACTIONS WITH OTHER MEDICINES

Concomitant Diuretic Therapy

When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients on diuretics, especially those on recently instituted diuretic therapy or in those with intravascular volume depletion, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with quinapril. The possibility of hypotensive effects with quinapril may be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to initiation of treatment with quinapril. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised (see **DOSAGE AND ADMINISTRATION**).

Agents Increasing Serum Potassium

Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. The concomitant therapy of an ACE inhibitor with potassium-sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, potassium-containing salt substitutes, or other drugs known to raise serum potassium levels can increase the risk of hyperkalaemia. Therefore if co-administration is indicated they should be used with caution and patient's serum potassium should be monitored frequently. In patients who are elderly or have compromised renal function, co-administration of an ACE inhibitor with sulfamethoxazole/trimethoprim has been associated with severe hyperkalaemia, which is thought to be due to trimethoprim. Quinapril and trimethoprim-

containing products should therefore be co-administered with caution and with appropriate monitoring of serum potassium.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)

Dual blockade of the RAAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalaemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function and electrolytes in patients on quinapril and other agents that affect the RAAS (see **PRECAUTIONS**).

Do not administer quinapril in combination with aliskiren in patients with diabetes, in patients with moderate to severe renal impairment (GFR <60 mL/min/1.73 m²), in patients with hyperkalaemia (>5 mmol/L) or in congestive heart failure patients who are hypotensive (see **CONTRAINDICATIONS**).

Do not administer quinapril in combination with angiotensin receptor blockers or other ACE inhibitors in diabetic patients with end organ damage, in patients with moderate to severe renal impairment (GFR <60 mL/min/1.73 m²), in patients with hyperkalaemia (>5 mmol/L) or in congestive heart failure patients who are hypotensive (see **CONTRAINDICATIONS**).

Tetracycline and Other Drugs that Interact with Magnesium

Simultaneous administration of tetracycline with quinapril reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in AQUINAFIL tablets. This interaction should be considered if co-prescribing AQUINAFIL and tetracycline or other drugs that interact with magnesium.

Lithium

Increased serum lithium and symptoms of lithium toxicity have been reported in patients receiving lithium concomitantly with drugs which cause elimination of sodium, including ACE inhibitors. These drugs should be co-administered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Non-steroidal Anti-inflammatory Agents Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

Non-steroidal anti-inflammatory drugs with prostaglandin synthetase inhibitory properties (e.g. indomethacin) may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including quinapril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving quinapril and NSAID therapy.

The antihypertensive effect of ACE inhibitors, including quinapril, may be attenuated by NSAIDs.

Other Drugs Known to Cause Angioedema

Patients taking concomitant mTOR inhibitor (e.g. temsirolimus) or concomitant DPP-IV inhibitor (e.g. vildagliptin) therapy or a neutral endopeptidase inhibitor may be at increased risk for angioedema. Caution should be used when starting an mTOR inhibitor or a DPP-IV inhibitor or a neutral endopeptidase inhibitor (see **CONTRAINDICATIONS**) in a patient already taking an ACE inhibitor.

Agents Affecting Sympathetic Activity

Agents affecting sympathetic activity (e.g. ganglionic blocking agents or adrenergic neurone blocking agents) may be used with caution. Beta-adrenergic blocking drugs will increase the antihypertensive effect of ACE inhibitors, and therefore the patient will need to be closely supervised.

Other Agents

Drug interaction studies of quinapril with other agents showed:

Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of quinapril.

The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril co-administration twice daily.

Quinapril treatment did not affect the pharmacokinetics of digoxin.

No pharmacokinetic interaction was observed when single doses of quinapril and hydrochlorothiazide were administered concomitantly.

ADVERSE EFFECTS

Hypertension

Quinapril has been evaluated for safety in 4960 subjects and patients and was well tolerated. Of these, 3203 patients including 655 elderly patients, participated in controlled clinical trials. Quinapril has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient in nature. Discontinuation of therapy because of adverse events was required in 4.7% of patients in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with quinapril are shown below.

Adverse Events in Placebo-Controlled Trials

	Quinapril (n=1563) Incidence (Discontinuance) %	Placebo (n=579) Incidence (Discontinuance) %
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing [∞]	2.0 (0.5)	0.0
Nausea and/or vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal pain	1.0 (0.2)	0.7

[∞]See **PRECAUTIONS, Cough.**

Heart Failure

Quinapril has been evaluated for safety in 1222 quinapril treated patients. Of these, 632 patients participated in controlled trials. In placebo-controlled trials, discontinuation of therapy because of adverse events was required in 6.8% of patients with congestive heart failure.

Adverse experiences probably or possibly related or of unknown relationship to therapy occurring in 1% or more of the 585 patients in placebo-controlled congestive heart failure trials who were treated with quinapril are shown below.

Adverse Events in Placebo-Controlled Trials

	Quinapril (n=585) Incidence (Discontinuance) %	Placebo (n=295) Incidence (Discontinuance) %
Dizziness	7.7 (0.7)	5.1 (1.0)
Coughing [∞]	4.3 (0.3)	1.4
Hypotension	2.9 (0.5)	1.0
Fatigue	2.6 (0.2)	1.4
Nausea and/or vomiting	2.4 (0.2)	0.7
Chest pain	2.4	1.0
Dyspnoea	1.9 (0.2)	2.0
Diarrhoea	1.7	1.0
Headache	1.7	1.0 (0.3)
Myalgia	1.5	2.0
Rash	1.4 (0.2)	1.0
Back pain	1.2	0.3

[∞]See **PRECAUTIONS, Cough.**

Hypertension and/or Heart Failure

Clinical adverse experiences probably, possibly or definitely related, or of uncertain relationship to therapy occurring in 0.5% to ≤1.0% (except as noted) of the patients with congestive heart failure or hypertension treated with quinapril (with or without concomitant

diuretic) in controlled or uncontrolled trials (n=4847) and less frequent, clinically significant events seen in clinical trials or post-marketing experience listed by body system include:

Blood and lymphatic system disorders	Agranulocytosis, haemolytic anaemia, thrombocytopenia
Cardiac disorders	Angina pectoris, cardiac rhythm disturbances, cardiogenic shock, heart failure, hyperkalaemia, myocardial infarction, palpitations, tachycardia
Congenital, familial and genetic disorders	See CONTRAINDICATIONS and PRECAUTIONS, Use in Pregnancy
Eye disorders	Amblyopia
Gastrointestinal disorders	Constipation, dry mouth or throat, flatulence, gastrointestinal haemorrhage, pancreatitis
General disorders and administration site conditions	Oedema (peripheral and generalised)
Hepatobiliary disorders	Hepatitis
Immune system disorders	Anaphylactoid reactions
Infections and infestations	Pharyngitis
Investigations	Abnormal liver function tests
Musculoskeletal and connective tissue disorders	Arthralgia
Nervous system disorders	Cerebrovascular accident, somnolence, vertigo
Psychiatric disorders	Depression, nervousness
Renal and urinary disorders	Acute renal failure, urinary tract infection, worsening renal failure (see PRECAUTIONS)
Reproductive system and breast disorders	Impotence
Respiratory, thoracic and mediastinal disorders	Eosinophilic pneumonitis
Skin and subcutaneous tissue disorders	Alopecia, angioedema [#] , dermatopolymyositis, exfoliative dermatitis, increased perspiration, pemphigus, photosensitivity reaction, pruritus, rash
Vascular disorders	Hypertensive crisis, orthostatic hypotension, syncope, vasodilatation

Angioedema (0.1%) was reported in patients receiving quinapril. Angioedema associated with laryngeal oedema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with quinapril should be discontinued and appropriate therapy instituted immediately (see **PRECAUTIONS**).

Laboratory Findings

Haematology	See PRECAUTIONS
Hyperkalaemia	See CONTRAINDICATIONS and PRECAUTIONS
Hyponatraemia	See PRECAUTIONS
Creatinine and blood urea nitrogen	Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of the patients treated with quinapril alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on quinapril alone. These increases often reversed on continued therapy (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

AQUINAFIL should preferably be taken before meals as food with a high fat content may diminish the rate and extent of absorption of the drug.

Hypertension

Monotherapy

The recommended initial dosage of AQUINAFIL in patients not on diuretics is 5 to 10 mg once daily. Dosage should be adjusted according to blood pressure response measured at peak (2 to 6 hours after dosing) and trough (predosing). Generally, dosage adjustments should be made at intervals of at least 4 weeks. Most patients have required dosages of 10 to 40 mg/day, given as a single dose or in two equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients an increase in dosage or twice daily administration may be warranted. When a dose of 20 mg/day is reached without adequate response, a diuretic may be added (e.g. hydrochlorothiazide 12.5 or 25 mg) or if the dose is increased, optimal control may require twice daily medication.

Concomitant Diuretics

If blood pressure is not adequately controlled with AQUINAFIL monotherapy, a diuretic may be added. In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of AQUINAFIL. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued 2 to 3 days prior to beginning therapy with AQUINAFIL (see **PRECAUTIONS**). Then, if blood pressure is not controlled with AQUINAFIL alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 to 5 mg AQUINAFIL should be used with careful medical supervision for several hours and until blood pressure has stabilised.

The dosage should subsequently be titrated (as described above) to the optimal response (see **INTERACTIONS WITH OTHER MEDICINES**).

Use in Renal Impairment

Kinetic data indicate that the apparent elimination half-life of quinaprilat increases as creatinine clearance decreases. Recommended starting doses, based on clinical and pharmacokinetic data from patients with renal impairment, are as follows:

Creatinine Clearance	Maximum Recommended Initial Dose
>60 mL/min	10 mg
30 – 60 mL/min	5 mg
10 – 30 mL/min	2.5 mg
<10 mL/min	Insufficient data for dosage recommendation

Patients should subsequently have their dosage titrated (as described above) to the optimal response.

Use in the Elderly (≥65 years)

The recommended initial dosage of AQUINAFIL in elderly patients is 10 mg given once daily followed by titration (as described above) to the optimal response.

Congestive Heart Failure

AQUINAFIL is indicated as an adjunctive therapy with diuretics and/or cardiac glycosides. The recommended initial dosage in patients with congestive heart failure is a single 5 mg dose following which the patient should be monitored closely for symptomatic hypotension. If the initial dose of AQUINAFIL is well tolerated, patients may be titrated slowly at weekly intervals given as a divided dose twice a day up to 20 mg/day. Those patients who have received 10 mg twice daily during 1 month with satisfactory response may be transferred to 20 mg once daily. Few patients may require 40 mg/day given in two doses. Titration to higher doses should cease after an effective dose is reached or undesirable hypotension, or orthostatis, or azotaemia prohibits reaching this dose (see **PRECAUTIONS**). Patients can normally be maintained effectively on doses of 10 to 20 mg/day given as 1 or 2 doses. AQUINAFIL should always be given with concomitant diuretic and/or cardiac glycoside therapy.

Following the initial dose of AQUINAFIL, the patient should be observed under medical supervision for at least 2 hours for the presence of hypotension or orthostasis and, if present, until blood pressure stabilises. The appearance of hypotension, orthostasis, or azotaemia early in dose titration should not preclude further careful dose titration. Consideration should be given to reducing the dose of concomitant diuretics.

Dosage Adjustment in Patients with Heart Failure and Renal Impairment or Hyponatraemia

Pharmacokinetic data indicate that quinapril elimination is dependent on level of renal function in patients with heart failure and renal impairment. The recommended initial dose of AQUINAFIL is 5 mg in patients with creatinine clearance above 30 mL/min and 2.5 mg in patients with a creatinine clearance of 10 to 30 mL/min. There is insufficient data for dosage

recommendation in patients with creatinine clearance less than 10 mL/min (see **INTERACTIONS WITH OTHER MEDICINES**).

OVERDOSAGE

No specific information is available on the treatment of overdose with quinapril.

Signs and Symptoms

The most likely clinical manifestation would be symptoms attributable to severe hypotension. Survival has been reported in a 24-year-old male who presented with acute renal failure after intentionally ingesting 150 to 200 mg of quinapril. The patient recovered without haemodialysis.

Treatment of Overdosage

Treatment is symptomatic and supportive, consistent with established medical care. Hypotension would normally be treated by intravenous volume expansion, such as an infusion of normal saline. Persistent hypotension should be treated by established procedures. Laboratory determinations of serum levels of quinapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of quinapril overdose.

No data are available to suggest physiological manoeuvres (e.g. manoeuvres to change pH of the urine) that might accelerate elimination of quinapril and its metabolites would be effective.

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

Contact the Poisons Information Centre on 131126 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

5 mg tablet: Reddish-brown, oval, biconvex, film-coated tablet, with bisecting score on both sides and debossing “5” on both sides in opposite direction; blister pack of 30s.

10 mg tablet: Reddish-brown, triangular, biconvex film-coated tablet, with bisecting score on both sides and debossing “10” on one side; blister pack of 30s.

20 mg tablet: Reddish-brown, round, biconvex film-coated tablet, with bisecting score on both sides and debossing “20” on one side; blister pack of 30s.

Not all pack sizes are distributed in Australia.

Storage

Tablets should be stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 5000 8422 348
38-42 Wharf Road
West Ryde NSW 2114.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

16 February 2011.

DATE OF MOST RECENT AMENDMENT

5 September 2017

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