AUSTRALIAN PRODUCT INFORMATION

MONACE

fosinopril sodium tablets

1 NAME OF THE MEDICINE

Fosinopril sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Monace tablet contains 10 mg or 20mg of fosinopril sodium as the active ingredient.

List of excipients with known effect: Monace tablets also contain traces of benzoates and sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

MONACE 10: Fosinopril sodium 10 mg tablets; white to off-white, arc-rectangular shaped, with "G | G" on one side and "FS | 10" on the other side.

MONACE 20: Fosinopril sodium 20 mg tablets; white to off-white, capsule shaped, with "G | G" on one side and "FS | 20" on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypertension:

Monace is indicated in the treatment of mild to moderate hypertension.

Monace is effective alone as initial therapy or in combination with other antihypertensive agents. The antihypertensive effects of Monace and diuretics used concomitantly are approximately additive.

Data have not been provided to support the use of Monace in severe or renovascular hypertension.

Heart Failure

Monace is indicated for the management of heart failure when added to conventional therapy, including diuretics.

4.2 DOSE AND METHOD OF ADMINISTRATION

Hypertension

For Hypertensive Patients Not Being Treated With Diuretics:

The recommended initial dose of Monace is 10 mg once a day. The usual dose range required to maintain blood pressure control is 10 to 40 mg per day administered as a single dose. Monace should be taken at the same time each day. Dosage should then be adjusted according to blood pressure response. If blood pressure is not adequately controlled with Monace alone, a diuretic may be added.

For Hypertensive Patients Currently Being Treated With Diuretics (or who may be volume depleted):

The diuretic should preferably be discontinued for several days prior to beginning therapy with Monace in order to reduce the risk of an excessive hypotensive response (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). If blood pressure is inadequately controlled after an observation period of approximately 4 weeks, diuretic therapy may be resumed. Alternatively, if diuretic therapy cannot be discontinued, an initial dose of 10 mg of Monace should be used with careful medical supervision for several hours and until blood pressure has stabilised (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Since concomitant administration of Monace with potassium supplements, potassium containing salt substitutes or potassium-sparing diuretics may lead to increases in serum potassium, they should be used with caution.

Heart Failure

The recommended initial dose of Monace is 10 mg once daily. Therapy should be initiated under close medical supervision. If the initial dose of Monace is well tolerated, the dose may be titrated at weekly intervals according to clinical response up to 40 mg once daily. The appearance of hypotension after the initial dose should not preclude careful dose titration with Monace following effective management of hypotension. Monace should be used in conjunction with a diuretic (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hypotension).

For Patients with Renal Impairment

In patients with impaired renal function, the total body clearance of fosinopril diacid is approximately 50% slower than in patients with normal renal function. However, within the population of renally impaired patients, the body clearance of fosinopril diacid does not differ appreciably with the degree of renal insufficiency, including end-stage renal failure (creatinine clearance <10 mL/min/1.73 m^2), since diminished renal elimination is partially compensated by increased hepatobiliary elimination. The relatively greater clearance by the hepatobiliary route of active fosinopril diacid when compared with total clearance in patients with renal failure permits use of an initial dose of 5 to 10 mg. An initial dose of 5 mg is preferred in heart failure patients with moderate to severe renal failure or those who have been vigorously diuresed. In patients with congestive heart failure and chronic renal failure, subsequent dosage adjustments should be made to control the patient's heart failure under careful clinical monitoring including frequent determination of renal function.

For Patients with Hepatic Insufficiency

It is advisable to initiate treatment at a dose of 10 mg in patients with mild to moderate impairment. Although the rate of hydrolysis of fosinopril diacid may be slowed, the extent of hydrolysis is not appreciably reduced in patients with hepatic impairment. In this group of patients, there is evidence of reduced hepatic clearance of fosinopril diacid with compensatory increase in renal excretion.

4.3 CONTRAINDICATIONS

Monace is contra-indicated in patients who are hypersensitive to fosinopril sodium, or to any other angiotensin converting enzyme inhibitor (e.g. a patient who has experienced angioedema during therapy with any other ACE inhibitor) or to any of the Monace tablet excipients.

Patients with history of hereditary and/or idiopathic angioedema or angioedema associated with previous treatment with an angiotensin converting enzyme inhibitor.

Monace is contra-indicated in pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy).

The concomitant use of ACE inhibitor with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR <60 mL/min/1.73m^2) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Anaphylactoid and Possibly Related Reactions

Head and neck angioedema:

Severe life threatening angioedema has been reported rarely with angiotensin converting enzyme (ACE) inhibitors. The overall incidence is approximately 0.1% to 0.2%. There seems to be no sex difference in the incidence of angioedema or in the predisposition to angioedema in patients with heart failure or hypertension. In the majority of reported cases, the symptoms occurred during the first week of therapy. However, the onset

of angioedema may be delayed for weeks or months. Patients may have multiple episodes of angioedema with long symptom-free intervals. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Angioedema may occur with or without urticaria but usually the angioedema involves non-pitting oedema of the skin and oedema of the subcutaneous tissues and mucous membranes.

Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with ACE inhibitors, including fosinopril. In such cases, the product should be discontinued promptly and appropriate monitoring instituted to ensure complete resolution of symptoms. In instances where swelling has been confined to the face and lips, the angioedema has generally resolved either without treatment or with anti-histamines. Angioedema associated with laryngeal oedema is potentially life-threatening. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur and can be fatal. Emergency therapy, including but not necessarily limited to adrenaline (epinephrine) and oxygen administration, should be carried out promptly or the patient hospitalised. Patients who respond to medical treatment should be observed carefully for a possible re-emergence of symptoms of angioedema.

There are reports where changing the patient over 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 Section 4.3 CONTRAINDICATIONS).

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-black patients.

Patients receiving coadministration of ACE inhibitor and mTOR (mammalian target of rapamycin) inhibitor (e.g. temsirolimus, sirolimus, everolimus) or vildagliptin therapy may be at increased risk for angioedema.

Intestinal angioedema:

Intestinal angioedema has been reported rarely in patients treated with ACE-inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior history of facial angiooedema and C-1 esterase levels were normal. The angioedema was diagnosed by procedures including CT scans 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.

Anaphylactoid reactions during desensitisation:

Two patients undergoing desensitising treatment with hymenoptera venom while receiving another ACE inhibitor, enalapril, sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when the ACE inhibitor was temporarily withheld, but they reappeared upon inadvertent rechallenge. Therefore, caution should be used in patients treated with ACE inhibitors undergoing such desensitisation procedures.

Anaphylactoid reactions during high-flux dialysis/lipoprotein apheresis membrane exposure:

Patients haemodialysed using high-flux polyacrylonitrile ("AN69") membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors.

Anaphylactoid reactions have also been reported in patients undergoing low density lipoprotein apheresis with dextran sulfate adsorption. These combinations should therefore be avoided, either by use of a different class of medication or alternative membranes (e.g. cuprophane or polysulphone PSF for haemodialysis).

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, immunodepressant 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 micromol/L) and those on multiple drug therapy with agents known to be nephrotoxic or myelosuppressive.

Hypotension

Monace can cause symptomatic hypotension. Like other ACE inhibitors, fosinopril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with Monace. A transient hypotensive response is not a contra-indication to further doses which may be given without difficulty after replacement of salt and/or volume.

The risk of an exaggerated hypotensive response (and also hyponatraemia) can be minimised by discontinuing the diuretic and ensuring adequate hydration and salt intake prior to initiation of treatment with fosinopril. If diuretics are continued, the patient should be closely observed for several hours following an initial dose and until blood pressure has stabilised.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotaemia and, rarely, with acute renal failure and death. In such patients, Monace therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of fosinopril or diuretic is increased.

Consideration should be given to reducing the diuretic dose in patients with normal or low blood pressure who have been treated vigorously with diuretics or who are hyponatraemic. Hypotension is not per se a reason to discontinue fosinopril. Some decrease of systemic blood pressure is not an uncommon observation upon initiation of Monace treatment in heart failure. The magnitude of the decrease is greatest early in the course of treatment; this effect stabilises within a week or two, and generally returns to pretreatment levels without a decrease in therapeutic efficacy.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with intravenous infusion of physiological saline. Monace treatment usually can be continued following restoration of blood pressure and volume.

Hepatic Failure

Rarely, ACE inhibitors have been associated with the syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical attention.

Hyperkalaemia

Because the ACE inhibitors decrease the formation of Angiotensin II, which results in decreased production of aldosterone, increase in serum potassium levels (>5.5 mEq/L) are not unexpected with this class of drugs. Hyperkalaemia is more likely in patients with some degree of renal impairment, those treated with potassium sparing diuretics or potassium supplements and/or consuming potassium containing salt substitutes, or those patients taking other medicines associated with an increase in serum potassium (e.g. trimethoprim containing medicines). Diabetics, and particularly elderly diabetics, may be at increased risk of hyperkalaemia. In some patients, hyponatraemia may coexist with hyperkalaemia. It is recommended that patients undergoing ACE inhibitor treatment should have measurement of serum electrolytes (including potassium, sodium and urea) from time to time. This is more important in patients taking diuretics.

Cough

A persistent dry (non-productive) irritating cough has been reported with all ACE inhibitors in use. The frequency of reports has been increasing since cough was first recognised as a side-effect of ACE inhibition. In various studies, the incidence of cough varies between 2% to >9% depending upon the drug, dosage and duration of use.

The cough is often worse when lying down or at night. The cough is commoner in women (who account for 2/3 of the reported cases). Patients who cough may have increased bronchial reactivity compared to those who do not cough. The observed higher frequency of this complication in non-smokers may be due to higher level of tolerance to cough by smokers.

The mechanism of this adverse reaction is not clear but most likely to be secondary to the effects of converting-enzyme inhibitor on kinins (bradykinin and/or prostaglandin) resulting in stimulation of pulmonary cough reflex. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor. The reaction may recur on rechallenge with another ACE inhibitor but this is not invariably the case. A change in antihypertensive regime may be required in severe cases.

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 congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors may be associated with oliguria and/or progressive azotaemia but rarely with acute renal failure and/or death. In patients with congestive heart failure and pre-existing renal failure, fosinopril like other ACE inhibitors should be used with caution. Although available data suggests minimal accumulation during 10 days therapy with fosinopril 10 mg daily, dosage reduction in this patient group may be necessary and renal function should be closely monitored.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20 percent of patients. These increases are usually reversible upon discontinuation of ACE treatment and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine which is usually minor and transient, especially when given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic may be required.

ACE inhibitors have a real potential to delay progression of nephropathy in diabetic as well as in hypertensive patients. The antiproteinuric effect of ACE inhibitors could depend upon the dose, selective availability at the renal tissue site and on the patient's sodium status. Nevertheless, 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 the hypertensive patient should always include assessment of renal function (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). If a 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, another class of antihypertensive agent should be preferred.

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

There is evidence that the concomitant use of ACE inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes, and blood pressure. ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Surgery/Anaesthesia

In patients undergoing major surgery or anaesthesia who are being treated with agents that produce hypotension, ACE inhibitors may block Angiotensin II formation secondary to compensatory renin release

and may thus augment the hypotensive response. If hypotension occurs, and is considered to be due to this mechanism, it can be corrected by volume expansion.

Dermatological Reactions

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity has been reported with another ACE inhibitor. Rare and sometimes severe skin reactions (lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome etc.) have been reported. A causal relationship is difficult to assess.

Patients who developed a cutaneous adverse event with one ACE inhibitor may be free of reaction when switched to another drug of the same class, but there are also reports of cross-reactivity.

Taste Disturbance (Dysgeusia)

Taste disturbances were reported to be high (up to 12.5%) with high doses of another ACE inhibitor. The actual incidence of taste disturbance is probably low (<0.5%) but data in this respect is scarce and difficult to interpret.

Taste disturbances with ACE inhibitors are described as suppression of taste or a metallic sensation in the mouth. The dysgeusia occurs usually in the first weeks of treatment and usually disappears within 1-3 months of treatment.

Use in Hepatic Impairment

Patients with impaired liver function could develop elevated plasma levels of fosinopril. In a study in patients with alcoholic or biliary cirrhosis, the apparent total body clearance of fosinopril was decreased and the plasma AUC approximately doubled.

Use in the Elderly

No dosage reduction is necessary in patients with clinically normal renal and hepatic function as no significant differences in the pharmacokinetic parameters or antihypertensive effect of fosinopril diacid have been found compared with younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Paediatric Use

Safety and effectiveness in individuals less than 18 years old have not been established.

Effects on Laboratory Tests

Fosinopril may cause a false low measurement of serum digoxin levels with assays utilising the charcoal absorption method. Other kits which utilise the antibody coated-tube method may be used instead. Therapy with Monace should be interrupted for a few days before carrying out tests of parathyroid function.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Diuretics

Since the antihypertensive effects of ACE inhibitors are enhanced by diuretics, patients on diuretics, especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restrictions, dialysis or with intravascular volume depletion, may occasionally experience excessive blood pressure reduction or hypotensive symptoms (e.g., dizziness, etc.) with the initiation of ACE inhibitor therapy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Hypotension; Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Since increases in serum potassium have been observed with ACE inhibitors, including fosinopril, the potassium wasting effect of most diuretics may be blunted by concomitant ACE inhibitor therapy. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride) should be used with caution when administered concomitantly with ACE inhibitors. Monitor serum potassium in such patients frequently.

Decreases in serum sodium and increases in serum creatinine occurred more frequently in patients receiving concomitant diuretics than in those treated with fosinopril alone.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including COX-2 inhibitor) and a thiazide diuretic may increase the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy, and periodically thereafter.

Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered 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.

Hyperkalaemia

Potassium sparing diuretics, potassium supplements, potassium salts or other medicinal products that may increase serum potassium levels (e.g. trimethoprim containing medicines) can increase the risk of hyperkalaemia. These products should therefore be used with caution and serum potassium should be monitored frequently.

Anti-diabetics

ACE inhibitors, including captopril, can potentiate the blood glucose-reducing effects of insulin and oral anti-diabetics such as sulphonylurea in diabetics. Glycaemia levels should be monitored at the beginning of initiation therapy to adjust the dose of the anti-diabetic medications.

Patients taking concomitant vildagliptin may be at increased risk for angioedema.

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS acting agent (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Inhibitors of Endogenous Prostaglandin Synthesis

It has been reported that indometacin may reduce the antihypertensive effect of other ACE inhibitors, especially in cases of low renin hypertension. Other non-steroidal anti-inflammatory agents (e.g., aspirin) and selective COX-2 inhibitors may have a similar effect. 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 fosinopril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving fosinopril and NSAID therapy.

Antacids

In a clinical pharmacology study, co-administration of an antacid (aluminium hydroxide, magnesium hydroxide, and simethicone) with fosinopril reduced serum levels and urinary excretion of fosinopril diacid as compared with fosinopril administered alone, suggesting that antacids may impair absorption of fosinopril. Therefore, if concomitant administration of these agents is indicated, dosing should be separated by 2 hours.

Mammalian Target of Rapamycin (mTOR) Inhibitors

Patients taking concomitant mTOR inhibitor (e.g. temsirolimus, sirolimus, everolimus) therapy may be at increased risk of angioedema.

Other Agents

In pharmacokinetic interaction studies with nifedipine, propranolol, cimetidine, and metoclopramide and propantheline the bioavailability of fosinopril diacid was not altered by coadministration of fosinopril with

any one of these drugs. In studies with concomitant administration of aspirin and Monace, the AUC for unbound fosinopril diacid was not altered, however the AUC for total (bound and unbound) fosinopril diacid and 48 hour cumulatory urinary excretion were reduced by 42%.

In pharmacokinetic studies in healthy volunteers, no clinically significant interactions occurred when fosinopril was co-administered with either digoxin or warfarin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There were no adverse reproductive effects in male and female rats treated with 15 to 60 mg/kg daily. There was no effect on pairing time prior to mating in rats until a daily dose of 240 mg/kg, a toxic dose, was given; at this dose, a slight increase in pairing time was observed.

Use in Pregnancy (Category D)

As with all ACE inhibitors, Monace should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with Monace 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.

If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.

When used in pregnancy, ACE inhibitors can cause injury and even death to the developing foetus.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with foetal and neonatal injury including hypotension, neonatal skull hypoplasia anuria, reversible and irreversible renal failure and death.

Oligohydramnios has also been reported, presumably resulting from decreased foetal function; oligohydramnios has been associated with foetal limb contractures, craniofacial malformations, hypoplastic lung development, and intra-uterine growth retardation. Prematurity and patent ductus arteriosus have also been reported.

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 1st trimester compared to 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 to no exposure.

Use in Lactation

Ingestion of 20 mg daily for three days resulted in detectable levels of fosinopril diacid in human breast milk. Monace (fosinopril sodium) should not be administered to breastfeeding mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects such as hypotension, dizziness and fatigue may interfere with the ability to drive or operate machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Hypertension

Fosinopril has been evaluated for safety in more than 1500 individuals, including 300 patients treated for a year or more. In placebo-controlled clinical trials, the usual duration of therapy was two to three months.

In placebo-controlled clinical trials (633 fosinopril-treated patients) 3.3 percent of patients were discontinued from fosinopril and 1.2 percent from placebo due to any adverse experience.

Heart Failure

In placebo-controlled clinical trials of 3-6 month duration, the discontinuation rates due to any clinical or laboratory adverse event, except for heart failure, were 8.0% and 7.5% in fosinopril-treated and placebo-treated patients, respectively.

During clinical trials with any fosinopril regimen, the incidence of adverse experiences in the elderly (≥65 years old) was similar to that seen in younger patients.

Clinical adverse events (and consequent study discontinuations) occurring in patients treated with fosinopril alone in placebo-controlled trials are summarised in Table 1 below. The incidences in columns A and B represent all clinical adverse events, observed in hypertension trials regardless of their attribution to study therapy, that occurred in at least 1% of patients. Columns C and D give the incidences for clinical adverse events to therapy occurring in at least 1% of patients treated with fosinopril in placebo controlled trials in heart failure.

Table 1. Clinical Adverse Experiences in Placebo-Controlled Trials

	Incidence* % Regardless of Attribution in Hypertension Trials (Discontinuation)		**Incidence % (a) in Heart Failure Trials (Discontinuation)**	
	Fosinopril n=633 (A)	**Placebo n=172 (B)**	**Fosinopril n=361 (C)**	**Placebo n=373 (D)**
Body System/Event				
General				
Fatigue	4.1(0.6)	2.9		
Chest pain (b)	1.9(0.3)	1.2	2.2(0.0)	1.6(0.0)
Oedema	1.6(0.0)	2.4		
Viral infection	1.3(0.2)	0.6		
Pain	1.1(0.0)	0.6		
Weakness			1.4(0.3)	0.5(0.0)
Cardiovascular				
Rhythm Disturbances/Palpitations	1.8(0.2)	1.2	1.4(0.3)	0.8(0.0)
Hypotension			4.4(0.8)	0.8(0.0)
Orthostatic Hypotension			1.9(0.0)	0.8(0.0)
Angina Pectoris			1.1(0.3)	1.1(0.0)
Dermatologic				
Rash	2.2(0.0)	0.0	1.4(0.3)	2.1(0.3)
Gastrointestinal				
Nausea/Vomiting	4.3(0.5)	2.9	2.2(0.6)	1.6(0.3)
Diarrhoea	4.1(0.5)	2.9	2.2(0.0)	1.3(0.0)
Abdominal Pain	2.0(0.3)	2.4		
Pyrosis	1.9(0.0)	0.6		
Musculoskeletal/Connective Tissue				
Musculoskeletal Pain	6.0(0.2)	3.5		
Myalgia	2.8(0.2)	1.8		
Nervous System				
Headache	8.4(0.9)	11.0		

	Dizziness	3.8(0.0)	1.2	11.9(0.6)	5.4(0.3)
	Mood Change**	2.7(0.7)	1.8(1.2)		
	Paraesthesia	1.6(0.0)	0.0		
	Sleep Disturbance	1.4(0.2)	0.6		
Respiratory					
	Cough	7.1(0.2)	3.5	9.7(0.8)	5.1(0.0)
	Sinus Abnormality	4.6(0.0)	2.9		
	Upper Resp. Infection	4.1(0.0)	4.7		
	Rhinitis	3.8(0.0)	2.9		
	Pharyngitis	3.9(0.2)	1.7		
Special Senses					
	Eye Disturbances, Other	1.6(0.0)	1.2		
	Taste Alterations	1.6(0.0)	0.0		
	Vision Disturbances	1.0(0.0)	1.2		
Urogenital					
	Abnormal Urination ***	1.3(0.0)	1.2		
	Sexual Dysfunction	1.7(0.4)	1.2(0.6)		

* No significant differences between Fosinopril and placebo.
** Includes stress reaction and nervousness.
*** Includes changes in urinary frequency, polyuria and oliguria.

(a) Clinical adverse events probably, possibly or of uncertain relationship to therapy.
(b) In HF trials defined as "non cardiac".

Other clinical adverse experiences reported with fosinopril and other ACE inhibitors are listed below by body system.

General: Weakness, fever[1a], hyperhidrosis, ecchymosis.

Cardiovascular: Sudden death[1], cardiac/cardiorespiratory[1] arrest, shock (0.2%)[1] angina/myocardial infarction, cerebrovascular accident, hypertensive crisis, tachycardia, cardiac rhythm disturbances[1], flushing, peripheral vascular disease, peripheral oedema[1], hypertension[1] syncope[1], conduction disorder[1].

Hypotension, orthostatic hypotension, and syncope occurred in 0.1, 1.5 and 0.2%, respectively, of patients treated with fosinopril for hypertension. Hypotension or syncope was a cause for discontinuation of therapy in 0.3 percent of patients.

Dermatologic: Pruritus[1a], dermatitis, urticaria, photosensitivity.

Endocrine/Metabolic: Gout[1a], sexual dysfunction[1].

Foetal/ Neonatal Morbidity and Mortality: The use of ACE inhibitors during pregnancy has been associated with foetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased foetal renal function; oligohydramnios in this setting has been associated with foetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported. More recently, prematurity, patent ductus arteriosus and other structural cardiac malformations, as well as neurologic malformations, have been reported following exposure limited to the first trimester of pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Pregnancy)

Gastrointestinal: Bleeding, pancreatitis, hepatitis, tongue swelling, dysphagia, oral lesions, abdominal distension, appetite[1a]/weight change[1a], constipation[1a], flatulence[1a], dry mouth[1a].

Haematologic: Lymphadenopathy.

Immunologic: Angioedema[1a] (0.2%).

Musculoskeletal: Arthritis, myalgia[1a], weakness of an extremity[1a].

Nervous/Psychiatric: Equilibrium disturbance, memory disturbance, drowsiness, confusion, depression[1], paraesthesia[1], vertigo[1], behaviour change[1], tremor[1], cerebral infarction[1], transient ischaemic attack[1].

Respiratory: Dyspnoea, bronchospasm, pneumonia, pulmonary congestion, laryngitis/hoarseness, epistaxis, rhinitis[1], sinusitis[1], tracheobronchitis[1], pleuritis[1], chest pain[1].

A symptom-complex of cough, bronchospasm, eosinophilia has been observed in two patients treated with fosinopril.

Special Senses: Tinnitus, ear pain, vision disturbance[1], taste disturbance[1].

Urogenital: Renal insufficiency, prostate disorder, abnormal urination[1].

Laboratory Test Abnormalities: Leukopenia, neutropenia, eosinophilia, increased serum levels of liver function tests (transaminases, LDH, alkaline phosphatase and bilirubin), serum electrolytes: hyperkalaemia, hyponatraemia (refer also to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Diuretics).

Renal Function Tests: Elevations, usually transient and minor, of BUN and creatinine have been observed. In placebo-controlled clinical trials, there were no significant differences in the number of patients experiencing increases in serum creatinine (outside the normal range or 1.33 times the pre-treatment value) between the fosinopril and placebo treatment groups.

In placebo-controlled trials in hypertension, a urinary albumin ≥2+ or ≥2 times the pre-treatment value was seen in 2.8 percent of fosinopril-treated and none of the placebo-treated group. Increases in urinary albumin usually developed in patients with pre-existing proteinuria or diabetes and caused no clinical adverse effect.

Haematology: In controlled trials, a mean haemoglobin decrease of 0.13 g/dL was observed in fosinopril-treated patients. In individual patients decreases in haemoglobin or haematocrit were usually transient, small, and not associated with symptoms. No patient was discontinued from therapy due to the development of anaemia.

Other: Leucopenia and eosinophilia have been reported. Neutropenia (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Liver Function Tests: Elevations of transaminases, alkaline phosphatase and serum bilirubin have been reported. Fosinopril therapy was discontinued because of serum transaminase elevations in 0.7% of patients in hypertension studies. In the majority of cases, the abnormalities were either present at baseline or were associated with other aetiologic factors. In those cases which were possibly related to fosinopril therapy, the elevations were generally mild and transient and resolved after discontinuation of therapy.

[1] Clinical events probably or possibly related, or of uncertain relationship to therapy, occurring in 0.4 to 1% of patients (except as noted) treated with fosinopril in controlled clinical trials in heart failure (n=516) and less frequent, clinically significant events.

[1a] Seen both in hypertension and heart failure patients. In heart failure patients in the incidence described under [1].

Post-marketing Experience

During post-marketing surveillance, the following adverse reactions were detected:

Skin and subcutaneous tissue disorders: pemphigus, bullous pemphigoid.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No specific information is available on the treatment of overdosage with Monace; treatment should be symptomatic and supportive. Therapy with Monace should be discontinued and the patient closely monitored. Suggested measures include correction of hypotension by established procedures. Fosinopril is poorly removed from the body by haemodialysis or peritoneal dialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Monace (fosinopril sodium) is the sodium salt of fosinopril, the ester prodrug of a long-acting angiotensin converting enzyme (ACE) inhibitor, fosinopril diacid. Fosinopril is a sub-class of ACE inhibitors. It contains a phosphinate group that makes it different from other marketed ACE inhibitors.

In humans and animals, fosinopril sodium following absorption is hydrolysed to the pharmacologically active fosinopril diacid, a specific competitive inhibitor of angiotensin converting enzyme (ACE).

ACE, a peptidyldipeptidase, catalyses the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II. Angiotensin II is a potent vasoconstrictor and it also stimulates aldosterone secretion by the adrenal cortex, thereby contributing to sodium and fluid retention. The effects of fosinopril in hypertension appear to result primarily from inhibition of angiotensin II formation and decreased aldosterone secretion. Inhibition of ACE activity leads to decreased levels of angiotensin II, thereby resulting in diminished vasoconstriction, aldosterone secretion, peripheral vascular resistance, and sodium and fluid retention. Decreased levels of angiotensin II and the accompanying lack of negative feedback on renal secretion results in increases in plasma renin activity. Decreased level of aldosterone results in a small increase of serum potassium.

While the mechanism through which fosinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, fosinopril has an antihypertensive effect even in patients with low-renin hypertension. Although fosinopril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to ACE inhibitor monotherapy than non-black patients.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of fosinopril remains to be elucidated.
Administration of fosinopril to patients with mild to moderate hypertension has reduced both supine and standing blood pressures, usually without orthostatic effects. Symptomatic postural hypotension was infrequent, although it should be considered in salt and/or volume depleted patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Following oral administration of a single dose of fosinopril, the onset of an antihypertensive effect was seen within 1 hour and peak blood pressure reduction within 2 to 6 hours.

At the usual daily dose (10 to 40 mg/day), antihypertensive effects of fosinopril have been maintained for 24 hours. In some patients at lower doses, these effects may diminish toward the end of the dosing interval (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

For optimal blood pressure reduction, dosage may need to be adjusted during the early stages of treatment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

The antihypertensive effect of fosinopril has been shown to continue during long term therapy for at least 2 years.

As with other ACE inhibitors, abrupt withdrawal of fosinopril has not been associated with rapid increases in blood pressure.

The antihypertensive effects of fosinopril and diuretics used concurrently are approximately additive.

In patients with heart failure, the beneficial effects of fosinopril are thought to result primarily from suppression of the renin-angiotensin-aldosterone system; inhibition of the angiotensin converting enzyme produces decreases in both preload and afterload.

In heart failure patients fosinopril improves symptoms and exercise tolerance, reduces severity of heart failure, and decreases the frequency of hospitalisation for heart failure. The beneficial effect of fosinopril does not require the concomitant use of digoxin.

Clinical Trials

Serum ACE activity was inhibited by ≥90% at 2 to 12 hours after single doses of 10 to 40 mg of fosinopril. At 24 hours, serum ACE activity remained suppressed by 85%, 93% and 93% in the 10, 20 and 40 mg dose groups, respectively.

In haemodynamic studies in hypertensive patients, after three months of therapy, responses (changes in BP, heart rate, cardiac index, and PVR) to various stimuli (e.g. isometric exercise, 45° head-up tilt, and mental challenge) were unchanged compared to baseline, suggesting that fosinopril does not affect the activity of the sympathetic nervous system. Reduction in systemic blood pressure appears to have been mediated by a decrease in peripheral vascular resistance without reflex cardiac effects. Similarly, renal, splanchnic, cerebral, and skeletal muscle blood flow were unchanged compared to baseline, as was glomerular filtration rate.

In a double-blind, controlled trial among patients with heart failure treated with diuretics and with or without digoxin, the initial dose of fosinopril resulted in an acute decrease in pulmonary capillary wedge pressure (preload), and mean arterial blood pressure and systemic vascular resistance (afterload). Single daily doses of fosinopril, maintained the positive haemodynamic effects throughout the 24 hour dosing interval among patients completing 10 weeks of treatment. In addition, heart rate decreased from baseline and stroke volume index increased despite the reduced left ventricular filling pressure. No tachyphylaxis was seen.

Fosinopril improved exercise tolerance at 24 hours in two placebo-controlled studies (271 patients with heart failure treated with fosinopril once daily) of up to six-months duration, including one trial in which patients were not treated concomitantly with digoxin. Clinical manifestations of heart failure also improved, as measured by study withdrawals (risk reduction 66%, P<.001) or hospitalisations for worsening heart failure (risk reduction 66%, P=.001). Fosinopril reduced the need for additional diuretic to control symptoms of heart failure. Severity of heart failure, as measured by favourable changes in New York Heart Association classification and on symptoms of heart failure, including dyspnoea and fatigue, improved.
The effects of fosinopril on long-term mortality in heart failure have not been evaluated.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, fosinopril (the prodrug) is absorbed slowly. The absolute absorption of fosinopril averaged 36% of an oral dose. The primary site of absorption is the proximal small intestine (duodenum/jejunum). The extent of absorption of fosinopril is essentially unaffected (but the rate may be slowed) by the presence of food in the gastrointestinal tract.

After single and repeated doses, areas under serum concentration-time curves (AUC) and peak concentrations (C_{max}) were directly proportional to the dose of fosinopril. The time to reach C_{max} (T_{max}) was independent of dose, achieved in approximately three hours, and consistent with peak inhibition of the angiotensin I pressor response 3 to 6 hours following the dose.

Distribution

Fosinopril diacid is highly protein-bound (≥95%), has a relatively small volume of distribution, and negligible binding to cellular components in blood.

Metabolism

In healthy subjects and renally impaired patients, hydrolysis of fosinopril to the active fosinopril diacid is rapid and complete. This biotransformation probably occurs in the gastrointestinal mucosa and liver. Although the rate of hydrolysis may be slowed, the extent of hydrolysis is not appreciably reduced in patients with hepatic impairment.

After an oral dose of radiolabelled fosinopril to healthy subjects, 75% of radioactivity in plasma was present as active fosinopril diacid, 20-30% as a glucuronide conjugate of fosinopril diacid, and 1-5% as a p-hydroxy metabolite of fosinopril diacid. In urine, 75% of the drug excreted was fosinopril diacid, the remainder consisted primarily of the glucuronide conjugate of fosinopril diacid. Since fosinopril diacid is not biotransformed after intravenous administration, fosinopril (the prodrug) may actually be the substrate for the glucuronide and p-hydroxy metabolites. In rats, the p-hydroxy metabolite of fosinopril diacid is as potent an inhibitor of ACE as fosinopril diacid. As expected, the glucuronide conjugate of fosinopril diacid is devoid of ACE inhibitory activity.

Excretion

In healthy subjects, the terminal elimination half-life (T½) of an intravenous dose of fosinopril diacid was approximately 12 hours. In patients with heart failure, the effective T½ was 14 hours. In hypertensive patients with normal renal and hepatic function, who received repeated doses of fosinopril, the effective T½ for accumulation of fosinopril diacid averaged 11.5 hours.

Special populations

In patients with renal insufficiency (creatinine clearance <80 mL/min/1.73 m^2), the following pharmacokinetic alterations were noted in comparison with normals (Table 2).

Table 2. Pharmacokinetic alterations in patients with renal insufficiency

Fosinopril diacid (IV)	Normal(5)	Mild(6)	Moderate(6)	Severe(5)
Total Clearance (mL/min)	25.8	13.7	13.3	14.3
Renal Clearance (mL/min)	10.5	5.1	2.8	2.2
Non-renal Clearance (mL/min)	15.3	8.6	10.6	12.1
120 h Urinary Excretion (% dose)	41	41	21	15
120 h Faecal Excretion (% dose)	43	44	67	61
AUC (ng.h/mL)	5133	9747	9380	8401

Absorption, bioavailability and protein binding were not appreciably altered; in the quoted trial, non-renal excretion of IV fosinopril diacid did not increase in absolute terms, however the increased faecal excretion of the active compound partially compensated for the reduced renal clearance even in patients with end stage

renal failure (creatinine clearance < 10 mL/min/1.73 m^2). Therefore, dosage adjustment during the initial stages of treatment will depend on blood pressure response. The initial dose should be 5-10 mg (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).
Clearance of fosinopril diacid by haemodialysis and peritoneal dialysis averages 2% and 7%, respectively, of urea clearances.

In patients with hepatic insufficiency (alcoholic or biliary cirrhosis), the extent of hydrolysis of fosinopril is not appreciably reduced, although the rate of hydrolysis may be slowed; the apparent total body clearance of fosinopril is approximately one-half of that in patients with normal hepatic function.

In clinical studies of fosinopril, no overall differences in effectiveness or safety were observed between elderly (>65 years old) and younger patients. Additional clinical experience has not identified differences in response between elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out.

In a pharmacokinetic study comparing elderly (65-74 years old) and non-elderly (20-35 years old) healthy volunteers, there were no significant differences in pharmacokinetic parameters of fosinopril diacid.

Studies in animals indicate that fosinopril and fosinopril diacid do not cross the blood-brain barrier.

In lactating women, bioavailability parameters (AUC, C_{max}, T_{max}) for fosinopril diacid were similar to healthy males. Fosinopril diacid was detectable but not quantifiable in breast milk.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Neither fosinopril sodium nor the active fosinopril diacid was mutagenic in the Ames microbial mutagen test, the mouse lymphoma forward mutation assay, or a mitotic gene conversion assay. Fosinopril was also not genotoxic in a mouse micronucleus test in vivo and a mouse bone marrow cytogenetic assay in vivo.

In the Chinese hamster ovary cell cytogenic assay, fosinopril increased the frequency of chromosomal aberrations when tested without metabolic activation at a concentration that was toxic to the cells. However, there was no increase in chromosomal aberrations at lower drug concentrations without metabolic activation or at any concentration with metabolic activation.

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 to cause this effect with other ACE inhibitors 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.

In two-year studies involving both mice and rats at doses up to 400 mg/kg daily, there was no evidence of a carcinogenic effect.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Pregelatinised maize starch, microcrystalline cellulose, hyprolose, ethanol, crospovidone, sodium starch glycollate and glyceryl behenate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

MONACE 10: Store in the original container below 25°C.
MONACE 20: Store in the original container below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

MONACE 10: Available in PVC/PCTFE (Aclar)/Al blister packs and PP bottles in pack sizes of 14, 28, 30, 56 and 100.

MONACE 20: Available in PVC/PCTFE (Aclar)/Al blister packs and PP bottles in pack sizes of 14, 28, 30, 56 and 100.

*Some pack sizes may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

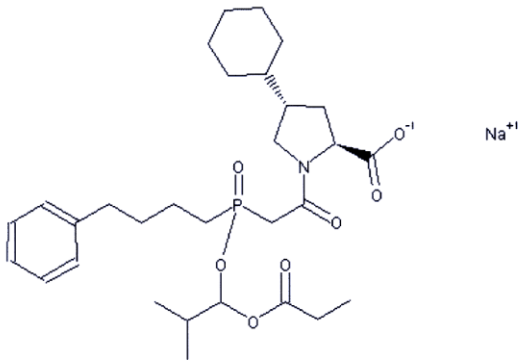
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : Sodium(4S)-4-cyclohexyl-1-{[(RS)-2-methyl-1-1-(propionyloxy)-proxoxyl]}(4-phenyl butyl)[phosphinoylacetyl]-1-proline

[1[S*(R*),2α,4β]-4-cyclohexyl-1-[[[2-methyl-1-(-oxopropoxy)propoxyl](4-phenylbutyl)phosphinyl]acetyl]-L-proline sodium salt

Structural formula :



Molecular formula : $C_{30}H_{45}NNaO_7P$

Molecular weight : 585.65

CAS Number

88889-14-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Limited

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

08/11/2005

10 DATE OF REVISION

13/11/2019

Summary Table of Changes

Section Changed	Summary of New Information
4.4, 4.5	Addition of interaction between ACE inhibitors and vildagliptin
4.4, 4.5	Updated precaution and interaction statements regarding hyperkalaemia, to include increases in serum potassium caused by other medicines
4.7	Updated to include adverse effects that may interfere with ability to drive or operate machinery

Monace_pi\Nov19/01