Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

Fosinopril Sodium 10mg Tablets

UK/H/910/01/MR

UK licence no: PL 00142/0582

Actavis UK Limited

Medicines and Healthcare products Regulatory Agency

LAY SUMMARY

A Marketing Authorisation (licence) for the medicinal product Fosinopril Sodium 10mg Tablets, to be marketed by Actavis UK Ltd, has been approved. This is a prescription-only medicine (POM) that is used for the treatment of hypertension (high blood pressure) and heart failure.

Fosinopril sodium tablets belong to a group of medicines called ACE inhibitors and make it easier for the heart to pump blood around the body.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Fosinopril Sodium 10mg Tablets outweigh the risks, hence Marketing Authorisation has been granted.

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Module 1

Product Name	Fosinopril Sodium 10mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Fosinopril Sodium
Form	Tablets
Strength	10mg
MA Holder	Actavis UK Limited Whiddon Valley Barnstaple, North Devon EX32 8NS United Kingdom
RMS	UK
CMS	Portugal
Procedure Number	UK/H/910/01/MR
Timetable	Day 90- 18/12/2006

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fosinopril Sodium 10mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of Fosinopril sodium

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, circular, flat, uncoated 8mm tablets marked 'FL 10'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension:
Fosinopril Sodium 10mg tablets are indicated in the treatment of hypertension. Fosinopril Sodium 10mg tablets may be used alone as initial therapy or in combination with other antihypertensive agents. The antihypertensive effects of Fosinopril Sodium 10mg tablets and diuretics used concomitantly are approximately additive.

Heart Failure:
Fosinopril Sodium 10mg tablets are indicated for the treatment of heart failure in combination with a non-potassium sparing diuretic and where appropriate, digitalis. In these patients, Fosinopril Sodium 10mg tablets improve symptoms and exercise tolerance, reduce severity of heart failure and decrease the frequency of hospitalisation for heart failure.

4.2 Posology and method of administration

Method of administration:
Oral

Posology

Hypertensive patients not being treated with diuretics:

The dose range is 10 to 40mg per day administered in a single dose and without regard to meals. The normal starting dose for patients is 10mg once a day. Dosage may need to be adjusted after approximately 4 weeks according to blood pressure response. No additional blood pressure lowering is achieved with doses greater than 40mg daily. If blood pressure is not adequately controlled with Fosinopril Sodium 20mg tablets alone, a diuretic can be added.

Hypertensive patients being treated with concomitant diuretic therapy:

The diuretic should preferably be discontinued for several days prior to beginning therapy with Fosinopril Sodium 20mg tablets to reduce the risk of an excessive hypotensive response. 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 should be used with careful medical supervision for several hours, until blood pressure has stabilised. In diuretic treated hypertensive patients, mean cerebral blood flow is maintained between 4 and 24 hours after fosinopril, despite significant reduction in blood pressure.

Heart Failure:

The recommended initial dose is 10mg once daily, initiated under close medical supervision. If the initial dose is well tolerated patients should then be titrated to a dose of up to 40mg once daily. The appearance of hypotension after the initial dose should not preclude careful dose titration of Fosinopril Sodium 20mg tablets, following effective management of the hypotension. Fosinopril Sodium 20mg tablets should be used in addition to diuretics and digitalis where appropriate.

Heart Failure - High Risk Patients:
It is recommended that treatment is initiated in hospital for patients with severe cardiac failure (NYHA IV) and those at particular risk of first dose hypotension, i.e. patients on multiple or high dose diuretics (e.g.> 80mg furosemide), patients with hypovolaemia, hyponatraemia (serum sodium < 130 meq/l), pre-existing hypotension (systolic blood pressure <90 mmHg), patients with unstable cardiac failure and those on high-dose vasodilator therapy.

CHILDREN

Fosinopril Sodium 20mg tablets should not be used in children under 18 years of age, as benefits have not been established.

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 fosinoprilat have been found compared with younger subjects.

IMPAIRED HEPATIC FUNCTION

Treatment should be initiated at a dose of 10mg. Although the rate of hydrolysis 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 fosinoprilat with compensatory increase in renal excretion.

RENAL IMPAIRMENT

Treatment should be initiated at a dose of 10mg. Depending on the response, the dose should then be titrated to achieve the desired therapeutic effect.

Absorption, bioavailability, protein binding, biotransformation and metabolism are not appreciably altered by reduced renal function. In patients with impaired renal function, the total body clearance of fosinoprilat is approximately 50% slower than that in patients with normal renal function. However, since hepatobiliary elimination compensates at least partially for diminished renal elimination, the body clearance of fosinoprilat is not appreciably different over a wide range of renal insufficiency (creatinine clearances ranging from <10 to 80 ml/min/1.73m^2, i.e. including end-stage renal failure).

Neither haemodialysis nor peritoneal dialysis is effective in clearing fosinoprilat. Peritoneal clearance is insignificant, ranging from 0.07 to 0.23ml per minute. Similarly haemodialysis for four hours clears only approximately 1.5% of the administered dose. This corresponds to 7% and 2% respectively, of urea clearance. Hence no dose adjustment is necessary to correct for drug loss during these procedures.

NB Fosinopril is NOT licensed for use in acute myocardial infarction.

4.3 Contraindications

- A history of hypersensitivity to fosinopril or any of the tablet excipients.
- History of angioneurotic oedema
- Renal artery stenosis (bilateral or unilateral in single kidney), and
- Cardiogenic shock.
- Pregnancy
- Lactation

4.4 Special warnings and precautions for use

WARNING

Hypotension: As with all ACE inhibitors, a hypotensive response may be observed. If this occurs it is usually associated with the first dose and in most instances, symptoms are relieved simply by the patient lying down. A transient, hypotensive episode is not a contraindication to continuing therapy once the patient's blood pressure has been stabilised.

As with other ACE inhibitors, patients at risk of an excessive hypotensive response, sometimes associated with renal dysfunction, include those with: congestive heart failure, renovascular hypertension, renal dialysis, or volume and/or salt depletion of any aetiology. In patients with any one of these risk factors, it may be prudent to discontinue or reduce the dose of diuretic therapy or take other measures to ensure adequate hydration prior to initiating fosinopril treatment. Treatment of these high risk patients should be initiated under careful medical supervision and they should be followed closely, particularly if it becomes necessary to resume or increase the dose of diuretic or Fosinopril Sodium 10mg Tablets.

Impaired Renal Function: When treated with ACE inhibitors, patients with pre- existing congestive heart failure, renovascular hypertension (especially renal artery stenosis), and salt or volume depletion of any aetiology are at increased risk of developing findings indicative of renal dysfunction, including: increases in BUN and serum creatinine and potassium; proteinuria; changes in urine volume (including oliguria/anuria); and an abnormal urinalysis. Dosage reduction and/or discontinuation of diuretic and/or fosinopril may be required.

Anaphylactoid-like Reactions: Recent clinical observations have shown a high incidence of anaphylactoid-like reactions during haemodialysis with high-flux dialysis membranes (e.g AN69) in patients receiving ACE inhibitors. Therefore, this combination should be avoided. Similar reactions during LDL aphoresis with dextran sulphate absorption have been observed. Rare instances of anaphylactoid reactions during desensitisation treatment (hymenoptera venom) have been recorded with other ACE inhibitors.

Idiosyncratic: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors. If such symptoms occur during treatment with Fosinopril Sodium 10mg Tablets, therapy should be discontinued.
Very rarely, fatalities have been reported due to angioedema associated with laryngeal oedema or tongue oedema. Patients with involvement of the tongue, glottis or larynx, are likely to experience airway obstruction, especially those with a history of airway surgery. In such cases emergency therapy should be administered promptly. This may include the administration of adrenaline (epinephrine) and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred.

Hepatic failure:
Very rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving Fosinopril sodium Tablets who develop jaundice or marked elevations of hepatic enzymes should discontinue Fosinopril sodium Tablets and receive appropriate medical follow-up.

Hyperkalaemia: When treated with ACE inhibitors, patients at risk of developing hyperkalaemia include those with renal insufficiency, diabetes mellitus, and those using concomitant potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes.

Neutropenia: ACE inhibitors have been reported rarely to cause reversible agranulocytosis and bone marrow depression; these occur more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Monitoring of white blood cell counts should be considered in such patients.

Surgery/Anaesthesia: ACE inhibitors may augment the hypotensive effects of anaesthetics and analgesics. If hypotension occurs in patients undergoing surgery/anaesthesia and concomitantly receiving ACE inhibitors, it can usually be corrected by intravenous administration of fluid.

PRECAUTIONS

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have sustained anaphylactoid reactions. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld but they have reappeared upon inadvertent re-administration of the medicinal product.

Cough

Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Diabetic patients

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see section 4.5)

Pre-treatment assessment of renal function: Evaluation of the hypertensive patient should include assessment of renal function prior to initiation of therapy and during treatment where appropriate.

Dialysis: See section 4.2 regarding use of fosinopril in patients receiving haemodialysis or peritoneal dialysis.

Aortic Stenosis, Mitral Stenosis and Hypertrophic Cardiomyopathy: In severe cases of these conditions where patients have fixed cardiac output, fosinopril may cause a large fall in blood pressure as such patients cannot compensate for the reduction in peripheral resistance with an increase in cardiac output.

Ethnic Factors: ACE inhibitors cause a higher rate of angioedema in black than in non-black patients. When fosinopril is given as a single agent in hypertension, Afro-Caribbean patients may show a reduced therapeutic response.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction

Potentially hazardous interactions:

Antacids: Antacids may impair absorption of fosinopril. Administration of Fosinopril Sodium 10mg Tablets and antacids should be separated by at least 2 hours.

NSAIDs: Non-steroidal anti-inflammatory drugs and more than 3g/day aspirin may interfere with the antihypertensive effect. However, the concomitant use of fosinopril and NSAIDs (including aspirin) is not associated with an increase in clinically significant adverse reactions. As with any ACE inhibitor, in some patients with compromised renal function the co-administration of fosinopril and NSAIDs may result in a further deterioration of renal function.

Lithium: Concomitant therapy with lithium may reversibly increase the serum lithium concentration.

Other Anti-Hypertensive Agents: Combination with other anti-hypertensive agents such as beta blockers, methyldopa, calcium antagonists, and diuretics may increase the anti-hypertensive effect.

Immunosuppressants: Concomitant use of fosinopril with immunosuppressants (e.g. azathioprine) may increase the risk of leucopenia developing.

Combinations not recommended:

Potassium supplements and potassium-sparing diuretics: Fosinopril can attenuate potassium loss caused by a thiazide diuretic. Potassium-sparing diuretics (e.g. spironolactone, amiloride or triamterene) or potassium supplements can increase the risk of hyperkalaemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution and the patient's serum potassium should be monitored frequently.

Other Drugs:

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicinal products (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

In pharmacokinetic studies with nifedipine, propranolol, cimetidine, metoclopramide and propantheline the bioavailability of fosinoprilat was not altered by coadministration of fosinopril with any one of these drugs.

Fosinopril has been used concomitantly with paracetamol, antihistamines, lipid-lowering agents or oestrogen without evidence of clinically important adverse events.

Laboratory tests: Fosinopril Sodium 10mg Tablets may cause a false low measurement of serum digoxin levels with assays using the charcoal absorption method for digoxin. Other kits which use the antibody coated-tube method may be used.

4.6 Pregnancy and lactation
Pregnancy: Fosinopril Sodium 10mg tablets are contraindicated in pregnancy. Fosinopril has been shown to be lethal to rabbit foetuses at doses that were maternally toxic. Oligohydramnios and neonatal hypotension and/or anuria have been reported following use of ACE inhibitors in the second and third trimester of pregnancy.

Lactation: Fosinopril Sodium 10mg tablets should not be given during lactation as fosinoprilat has been detected in human breast milk.

4.7 Effects on ability to drive and use machines
Whilst fosinopril is not expected to directly affect performance, it can cause adverse effects such as dizziness, vertigo or hypotension. Patients should make sure they are not affected before driving or operating machinery.

4.8. Undesirable effects

In the patients treated with Fosinopril sodium Tablets, the adverse effects were in general mild and transient.

Very common:	>1/10
Common:	>1/100 and <1/10
Uncommon:	>1/1000 and <1/100
Rare:	>1/10 000 and <1/1000
Very rare:	<1/10000 including isolated cases

Blood and lymphatic system disorders
Rare: Eosinophilia, leucopenia, lymphadenopathy, neutropenia, thrombocytopenia
Very rare: Agranulocytosis

Metabolism and nutrition disorders
Uncommon: Decreased appetite, gout, hyperkalaemia

Psychiatric disorders
Uncommon: Depression, confusion

Nervous system disorders
Common: Dizziness
Uncommon: Cerebral infarction, paraesthesia, somnolence, stroke, syncope, taste disturbances, tremor
Rare: Dysphasia, memory disturbances

Eye disorders
Uncommon: Visual disturbances

Ear and labyrinth disorders
Uncommon: Ear ache, tinnitus, vertigo

Cardiac disorders
Common: Tachycardia
Uncommon: Angina pectoris, myocardial infarction, palpitations, cardiac arrest, rhythm disturbances, conduction disturbances

Vascular disorders
Common: Hypotension, orthostatic hypotension
Uncommon: Hypertension, shock, transitory ischaemia
Rare: Flush, haemorrhage, peripheral vascular disease

Respiratory, thoracic and mediastinal disorders
Common: Cough
Uncommon: Dyspnoea, rhinitis, sinusitis, tracheobronchitis
Rare: Bronchospasm, epistaxis, laryngitis/ hoarseness, pneumonia, pulmonary congestion

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea
Uncommon: Constipation, dry mouth, flatulence
Rare: Oral lesions, pancreatitis, swollen tongue, abdominal distension, dysphagia

Hepatobiliary disorders
Rare: Hepatitis

Skin and subcutaneous tissue disorders
Common: Rash, angioedema, dermatitis
Uncommon: Hyperhidrosis, pruritus, urticaria
Rare: Ecchymosis

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia
Rare: Arthritis

Renal and urinary disorders
Uncommon: Renal failure
Rare: Prostatic disorders

Reproductive and breast disorders
Uncommon: Sexual dysfunction

General disorders and administration site conditions
Common: Chest pain (non-cardiac), weakness
Uncommon: Fever, peripheral oedema, sudden death, thoracic pain
Rare: Weakness in one extremity

Investigations
Common: Increase in alkaline phosphatase, increase in bilirubin, increase in LDH, increase in transaminases
Uncommon: Weight increase
Rare: Slight increase in haemoglobin

In the clinical studies performed with fosinopril, the incidence of adverse effects did not differ between elderly (more than 65 years of age) and younger patients.

4.9. Overdose

The symptoms of overdosage may include severe hypotension, electrolyte disturbance and renal failure. After ingestion of an overdose the patient should be kept under very close supervision.

Therapeutic measures depend on the nature and severity of the symptoms. Measures to prevent absorption and methods to speed elimination should be employed. If severe hypotension occurs the patient should be placed in the shock position and an intravenous infusion of normal saline given rapidly. Treatment with angiotensin II (if available) may be considered. The use of high-flux polyacrylonitrile dialysis membrane should be avoided. Serum electrolytes and creatinine should be monitored frequently.

Treatment overview:
- A. ACTIVATED CHARCOAL: Administer charcoal as a slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.

- B. HYPOTENSION: Infuse 10 to 20 mL/kg isotonic fluid, place in Trendelenburg position. If hypotension persists, administer dopamine (5 to 20 mcg/kg/min) or noradrenaline (norepinephrine) (0.1 to 0.2 mcg/kg/min), titrate to desired response.

- 1. Angiotensin infusion at doses ranging from 8.5 to 18 mcg/minute has been successful in reversing hypotension in patients who did not respond to volume and pressor infusions.

- 2. Naloxone has also been effective in some patients with hypotension.

- C. ANGIOEDEMA - Administer antihistamines and corticosteroids. Monitor airway carefully and administer oxygen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: CO9A A09 Pharmacotherapeutic group: ACE Inhibitors, plain.
Mechanism of action: Fosinopril is the pro-drug (ester) of the long acting active ACE inhibitor fosinoprilat. After oral administration fosinopril is quickly and fully metabolised to the active fosinoprilat. Fosinopril contains a phosphinic group capable of a specific binding to the active site of the angiotensin converting enzyme, preventing the conversion of angiotensin I in angiotensin II. The reduction in angiotensin II leads to a vasoconstriction reduction and a decrease in aldosterone secretion, which might induce a slight increase in serum potassium and a loss of sodium and fluid.
ACE inhibition also interferes with bradykinin degradation, a potent vasodepressant, contributing to the antihypertensive effect; fosinopril presents a therapeutic action in hypertensive patients with renin low levels.
In patients with cardiac failure, it is assumed that Fosinopril beneficial effects are mainly resultant of a suppression of the renin-angiotensin-aldosterone system; ACE inhibition produces a reduction in pre-load and post-load.
The onset of the anti-hypertensive effect is one hour after taking a single dose. The maximum effect is seen after 3-6 hours. With the usual daily dosage the anti-hypertensive effect lasts for 24 hours.
The blood pressure is reduced standing and in decubitus. The orthostatic effects and tachycardia are rare but might occur in patients with salt depletion or in hypovolemia. The blood pressure reduction might be progressive and several can be required to obtain the therapeutic effect.
Fosinopril and thiazide diuretics have additive effects.
In cardiac failure, fosinopril improves the symptoms and the exercise tolerance, reduces the severity of the cardiac failure and the frequency of the hospitalization due to cardiac failure.

5.2 Pharmacokinetic properties

Absorption
After oral administration, the extension of the absorption of fosinopril averages 30% to 40%. The absorption of fosinopril is not affected by the presence of food in gastrointestinal tract, however the speed of the absorption might be reduced. The time to reach the maximum plasma concentration is approximately three hours and is independent of administered dose. After multiple or single doses, the pharmacokinetic parameters (C_{max}, AUC) are directly proportional to the fosinopril dose that has been taken.
Distribution
Fosinoprilat is protein bound (> 95%), but has a negligible binding to blood cellular components.
Elimination
After intravenous administration, the elimination of fosinopril is by both hepatic and renal routes. In hypertensive patients that receive repeated doses of fosinopril and have normal renal and hepatic

functions, the fosinoprilat elimination half-life is 11.5 hours, being of 14 hours in patients with cardiac failure.
Special patient groups
In patients with renal failure (creatinine clearance < 80 ml/min/1,73 m^2), the total fosinoprilat body clearance is approximately half of that observed in patients with normal renal function, while no significant changes are seen in the absorption, the bioavailability and the plasma protein binding. The fosinoprilat clearance does not vary according with the degree of renal failure; the reduction in renal elimination is compensated by the increase in hepato-biliary elimination. A slight increase in AUC values (less than the double of normal values) has been observed in patients with several degrees of renal failure, including terminal renal failure (creatinine clearance < 10 ml/min/1.73 m^2).
In patients with hepatic failure (alcoholism or biliary cirrhosis), the fosinopril hydrolysis is not significantly reduced, although the rate of the hydrolysis might be reduced; the total fosinoprilat clearance is almost half of the clearance observed in patients with normal hepatic function.

5.3 Preclinical safety data
Animal studies indicate a toxicity profile which is an extension of the pharmacological effects of fosinopril. It has shown no evidence of carcinogenicity in rodent studies and no potential for mutagenicity in either *in vitro* or *in vivo* tests.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Also contains:
Lactose monohydrate
Pregelatinised starch
Croscarmellose sodium
Microcrystalline cellulose
Glycerol dibehenate.

6.2 Incompatibilities
None known.

6.3 Shelf life
18 months.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Aluminium-aluminium blisters
Each carton will contain either 7, 10, 14, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98, 100* tablets.

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Actavis UK Limited (Trading style: Actavis)
Whiddon Valley
BARNSTAPLE
N Devon EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)
PL 00142/0582

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17.01.05

10 DATE OF REVISION OF THE TEXT
16/07/2007

Module 3
Patient Information Leaflet

actavis

Fosinopril Sodium 10mg and 20mg Tablets

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

In this leaflet

1. What Fosinopril sodium is and what it is used for

Each tablet contains fosinopril sodium which is used to treat high blood pressure (hypertension) and heart failure. Fosinopril sodium tablets belong to a group of medicines called ACE inhibitors and make it easier for the heart to pump blood around the body.

2. Before you take Fosinopril sodium tablets

Do not take Fosinopril sodium tablets if you:
- are allergic (hypersensitive) to fosinopril sodium, other ACE inhibitors or any of the other ingredients in the tablet. (See Section 6 for further information on the ingredients)
- or a member of your family have previously had swelling of the legs, arms, face, mucous membranes or tongue and/or throat (angioedema), with or without ACE inhibitor treatment
- have narrowing of the blood vessels in one or both kidneys
- suffer from cardiogenic shock
- are pregnant or breastfeeding.

Take special care with Fosinopril sodium tablets

Tell your doctor of any medical problems you may have, or have previously had, especially if you:
- have kidney problems
- are having dialysis
- are going to undergo treatment for hypersensitivity to bee or wasp stings (hyposensitisation)
- have problems with your immune system due to some diseases (e.g. scleroderma, lupus erythematosus)
- have high levels of sugar in your blood (diabetes)
- have narrowing of some blood vessels in the heart or cardiomyopathy (enlarged heart muscle)
- have become dehydrated from having recently suffered from vomiting or diarrhoea
- are on a low salt diet.

Tell your doctor or dentist before undergoing any surgery or dental treatment that you are being treated with Fosinopril, as there is a risk of your blood pressure sinking very low during the anaesthetic.

Taking other medicines

If Fosinopril is taken with certain other medicines your treatment can be affected. Tell your doctor before using other medicines at the same time as Fosinopril. Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It is especially important for your doctor to know if you are already being treated with any of the following medicines:
- other blood pressure lowering medicines including methyldopa, betablockers (e.g. atenolol), calcium antagonists (e.g. verapamil) or diuretics (water tablets) (e.g. furosemide) as it may lead to an increase in the blood pressure lowering effects
- potassium-sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes, as Fosinopril may increase potassium levels
- painkillers and anti-inflammatory medicines of the NSAID type (e.g. aspirin or indometacin) as they can reduce the effect of Fosinopril
- antacids (to relieve indigestion) stop the body absorbing Fosinopril. There should be at least 2 hours between taking the antacid and Fosinopril
- insulin and tablets used in diabetes, as Fosinopril may increase the effect of these especially during the first week of combination treatment
- lithium (used for manic depression), as Fosinopril may increase the concentration of lithium in the blood
- immunosuppressants (these reduce the body's natural defence system) such as azathioprine as using them together may affect some blood counts.

Pregnancy and breast feeding

Do not take Fosinopril sodium tablets during pregnancy or if you might become pregnant. There is a risk of injury to the baby. Do not take Fosinopril if you are breast feeding, as Fosinopril crosses over into breast milk.

Driving and using machines

If you experience dizziness, low blood pressure, light-headedness or vertigo, do not drive or use machinery during treatment with Fosinopril.

Important information about some of the ingredients of Fosinopril

Fosinopril contains lactose (see section 6 for further information). If your doctor has told you that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Blood tests

Fosinopril may interfere with the results of some blood tests. Tell your doctor that you are taking Fosinopril sodium tablets.

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3. How to take Fosinopril sodium tablets

Swallow the tablets **whole** with at least ½ a glass of water in the morning **with or without food. Do not chew or crush the tablets.**

Always take Fosinopril exactly as your doctor has told you. If you are not sure check with your doctor or pharmacist.

Adults: The usual dose is 10mg once daily, up to a maximum of 40mg once daily. Fosinopril sodium tablets may be taken alone or in combination with a diuretic (water tablet) or digitalis (digoxin). If you are already taking diuretics, your doctor may tell you to reduce the dose of the diuretic or to stop taking them for several days before beginning treatment with Fosinopril.
Children under 18 years old: Not recommended.

Occasionally some people start their treatment in hospital.

If you take more Fosinopril sodium than you should:
Immediately contact your doctor, the nearest hospital casualty department or the centre for poison information for advice.

If you forget to take Fosinopril sodium
Do not take the missed dose, just carry on with the next one as normal. Do not take a double dose to make up for a forgotten dose.

If you stop taking Fosinopril sodium
Do not stop taking Fosinopril unless your doctor advises you to do so. If you stop taking Fosinopril, your blood pressure may increase.

4. Possible side effects

Like all medicines, Fosinopril can cause side effects, although not everybody gets them. **If you notice any of the following side effects or these side effects get worse, please tell your doctor:**

• **Common** (occurring in more than 1 in 100 users): dizziness, rise in heart rate, feeling faint on standing up due to reduced blood pressure, low blood pressure, cough, feeling or being sick, diarrhoea, rash, swelling, dermatitis, weakness, chest pain (not related to the heart), increase in blood levels of alkaline, bilirubin, LDH and transaminases (as seen in blood tests). **If you experience dizziness/fainting, tiredness or weakness especially on standing (symptoms of low blood pressure), contact your doctor as soon as possible.**

• **Uncommon** (occurring in less than 1 in 100 users): lack of appetite, gout, raised levels of potassium in the blood, depression, confusion, pins & needles, tremor, sleepiness, loss of consciousness, lack of blood supply to the brain, stroke, problems with sight, ear ache, vertigo, tinnitus (ringing in the ear), palpitations, chest pain (due to angina), heart attack, problems with heart rhythm, high blood pressure, shock, blocked blood vessels, upper airway symptoms, difficulty breathing, runny nose, inflamed sinus, constipation, dry mouth, weight gain, changes in taste, flatulence, excessive sweating, itchy rash, muscle and joint pain, kidney failure, problems with sexual function, fever, water retention, sudden death, pain in the upper body.
If you get swelling of the face, lips, tongue and/or throat, rash, itching, breathlessness or difficulty swallowing, you must stop taking Fosinopril and contact a doctor immediately.

• **Rare** (Occurs in between 1 in 10000 and 1 in 1000 people): changes in types and numbers of blood cells, memory and speech problems, flushing, bleeding, asthma, nosebleeds, sore throat, hoarseness, inflammation of the lungs, stomach pain, mouth ulcers, swollen tongue, swallowing difficulties, inflammation of the pancreas, inflammation of the liver, bruising, arthritis, prostate problems, weakness in one arm or leg.

Stop taking Fosinopril and contact your doctor immediately if you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with a sore throat/mouth or urinary problems. You may need a blood test.

If you have any of these side effects, they get worse, or you notice any side effects not listed, please tell your doctor or pharmacist.

5. How to store Fosinopril sodium tablets

Keep out of the reach and sight of children.
Do not store Fosinopril above 25°C.
Do not transfer to another container.

Do not use Fosinopril after the expiry date stated on the carton. The expiry date refers to the last day of that month.

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

6. Further information

What Fosinopril sodium tablets contain
- The active substance is fosinopril sodium. Each tablet contains either 10mg or 20mg of fosinopril sodium.
- The other ingredients are lactose monohydrate, croscarmellose sodium, pregelatinised starch (maize), microcrystalline cellulose and glycerol dibehenate.
- The sodium content is 0.67mg per 10mg tablet and 1.06mg per 20mg tablet.

What Fosinopril sodium tablets look like and contents of the pack
Fosinopril sodium tablets are white to off-white, round, uncoated tablets, which come in two strengths.
Each pack contains 28 tablets.

Marketing Authorisation Holder & Manufacturer:
Actavis, Barnstaple, EX32 8NS, UK

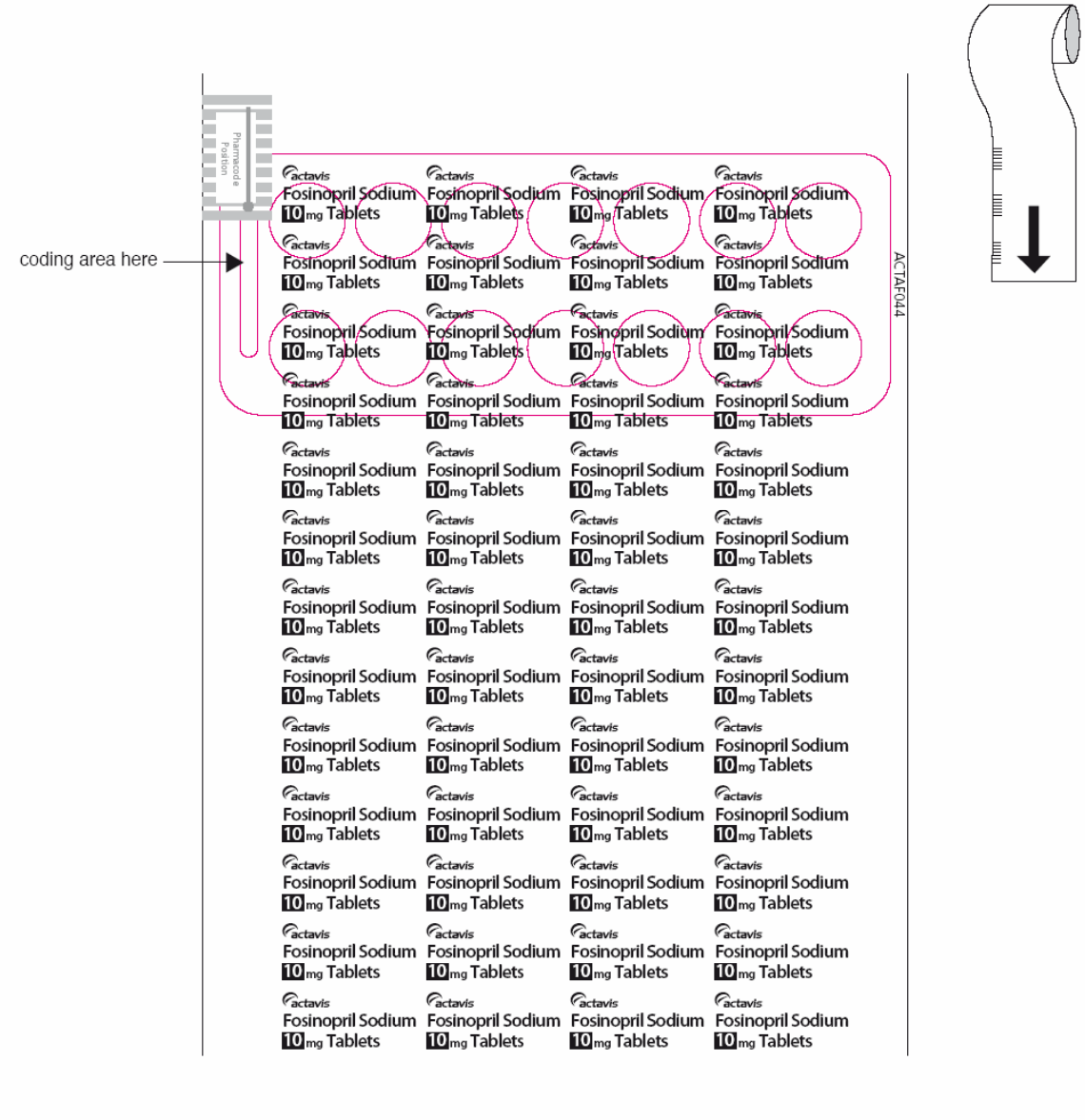
This leaflet was last revised in: August 2007

actavis
Actavis, Barnstaple, EX32 8NS, UK

ACTPL036

Module 4

Labelling




Fosinopril Sodium Tablets
28 tablets
10 mg
Each tablet contains 10mg Fosinopril sodium.
Also contains lactose. See leaflet for further information.
For oral use. Use as directed by physician.
Keep out of the reach and sight of children.
Do not store above 25°C.
Place dispensing label here
PL 0142/0582
POM
actavis
Actavis, Barnstaple, EX32 8NS, UK
Batch No.
Expiry date
ACTCN063
50x30x121
READ ENCLOSED LEAFLET
5 012617 014016
Braille reads:-
Fosinopril
Sodium
10 mg Tablets

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Fosinopril Sodium 10 mg Tablets in the treatment of the following indications could be approved:

Hypertension:
Fosinopril Sodium 10mg Tablets are indicated in the treatment of hypertension. Fosinopril Sodium 10mg Tablets may be used alone as initial therapy or in combination with other antihypertensive agents. The antihypertensive effects of Fosinopril Sodium 10mg Tablets and diuretics used concomitantly are approximately additive.

Heart Failure:
Fosinopril Sodium 10mg Tablets are indicated for the treatment of heart failure in combination with a non-potassium sparing diuretic and where appropriate, digitalis. In these patients, Fosinopril Sodium 10mg Tablets improve symptoms and exercise tolerance, reduce severity of heart failure and decrease the frequency of hospitalisation for heart failure.

A national marketing authorisation was granted on 17th January 2005.

This mutual recognition application concerns a generic version of Fosinopril Sodium Tablets.

The originator product was Staril Tablets 10 mg licensed to E R Squibb & Sons Limited (UK) on 3rd July 1990. Other licensed trade names are: Fositen 10 mg Tablets licensed to Bristol Myers Squibb (Portugal).

About the product

Fosinopril sodium is an anti-hypertensive agent that counteracts the vasopressor effects of angiotensin-II. It belongs to that subclass of ACEI that have dual modality of elimination, renal and hepatic, thereby reducing potential toxicity resulting from accumulation during either organ dysfunction. This prodrug undergoes metabolic transformation to its active form, Fosinoprilat after oral administration.

The development programme

The objective of the development programme was to develop a globally acceptable, stable and bioequivalent tablet dosage form of Fosinopril sodium comparable to Staril 10mg Tablets.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
No new preclinical studies were conducted, which is acceptable given that the application was based on generic medicinal product to the one that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on generic medicinal product. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

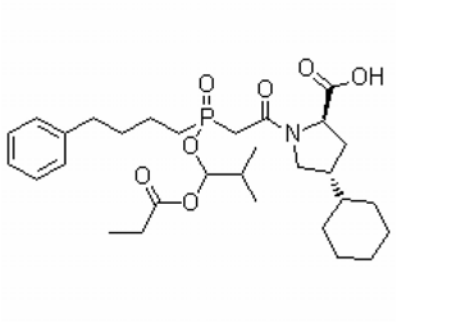
For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites

SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Nomenclature

Structure



Chemical name: 4-cyclohexyl-1-[2-[(2-methyl-1-propanoyloxy-propoxy)-(4-phenylbutyl)phosphoryl]acetyl] -pyrrolidine-2-carboxylic acid

Molecular Formula: $C_{30}H_{46}NO_7P$

Molecular Weight: 585.65

The drug substance is a white crystalline powder, freely soluble in water and methanol.

There are no pharmacopoeia monographs for this active. Appropriate specifications have been provided.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Active fosinopril sodium is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated, supporting the retest period of 2 years.

Drug Product

Description and Composition of the Drug product

Other ingredients consist of pharmaceutical excipients, namely Lactose Monohydrate, Pregelatinised Starch, Croscarmellose Sodium, Microcrystalline Cellulose, Glycerol Dibehenate, and Water Purified.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory specifications and Certificates of Analysis are provided for typical batches of excipients.

The only excipients used that contain material of animal or human origin are lactose monohydrate and Glycerol Dibehenate. The applicant has provided a declaration that milk used in the production of lactose anhydrous is sourced from healthy animals under the same conditions as that for human consumption. A TSE statement for Glycerol Dibehenate is also provided.

Dissolution

Dissolution and impurity profiles of drug product support the pharmaceutical equivalence of the applicant's product relative to the reference product.

Manufacture

The manufacturing process is adequately summarised and a flow diagram is provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out and the results of chemical and physical testing of the validation batches are satisfactory and show consistency and control in the manufacturing process.

Finished Product Specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data for tablets manufactured at the proposed manufacturing site demonstrate that the batches comply with the release specification. Satisfactory certificates of analysis are provided for the reference standards.

Container Closure System

The tablets are packed in aluminium blisters. The proposed aluminium foil is stated to be suitable for food and pharmaceutical use. Specifications and certificates of analysis are also provided for the packaging components and are satisfactory.

The blister strips are packed in cardboard cartons containing a total of:

• 7, 10, 14, 20, 21, 28, 30, 50, 56, 60, 84, 90, 98, and 100 Tablets.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 18 months when stored at 25 degree C has been set. This is acceptable.

CONCLUSIONS

Marketing Authorisation may be granted for this product.

PRE-CLINICAL ASSESSMENT

This application for a generic product claims essential similarity to Staril 10 mg Tablets, which has been licensed within the EEA for over 10 years.

No new preclinical data has been supplied with this application, however, a preclinical expert report summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a generic application for Fosinopril Sodium Tablets, submitted under directive 2001/83/EC, article 10.1 which is generic medicinal product to brand leader, Staril (ER Squibb & Sons; PL 00034/0292). Staril was authorised in July 1990 for use in hypertension and subsequently heart failure.

This 10 mg strength product was originally assessed in conjunction with Alpharma's 20 mg strength fosinopril sodium tablet (PL 00142/0583). However only the 10 mg strength is going through MRP at this time, the 20mg Strength has already been through an MR Procedure.

I.1 GCP aspects

A declaration has been provided that the bioequivalence study was conducted in accordance with GCP.

I.2 Orphan Medicinal Products

Not applicable:

I.3 Therapeutic Class

ATC Code: C09A A09, ACE inhibitor, Plain.
Fosinopril is, a phosphorus (phosphinate group) containing angiotensin converting enzyme inhibitor.

I.4 Background

Active

Fosinopril was first authorised in the UK in 1990 as Staril (BMS) as anti-hypertensive agent that counteracts the vasopressor effects of angiotensin-II. It belongs to that subclass of ACEI that have dual modality of elimination, renal and hepatic, thereby reducing potential toxicity resulting from accumulation during either organ dysfunction. This prodrug undergoes metabolic transformation to its active form, Fosinoprilat after oral administration.

Application

The current application is based on the principle of generic medicinal product demonstrated with a bioequivalence study (Directive 2001/83 EC, article 10.1. The reference compound is Staril (ER Squibb & Sons] and two bioequivalence studies have been carried out with Fosinorm 10mg tablets (Bristol-Myers-Squibb, Germany) and 20 mg Staril, (ER Squibb /BMS, UK).

I.5 Regulatory Status

Since 1990, Fosinopril (Staril or equivalent, BMS) has been authorised in several European countries including UK. In the UK, 7 formulations of Fosinopril have been authorised in doses of 10 and 20mg and approximately 40 parallel import licenses have been applied for. Fosinopril in combination with a thiazide diuretic has also received marketing authorisation for hypertension. [UK- PL: 11184/0037]. The 20mg tablet strength went through a mutual recognition procedure in 2005, and the Day 90 for this procedure was on the 1st of June 2005. The concerned member state for this procedure was Portugal.

I.6 Indications

Hypertension:

Fosinopril Sodium 10mg tablets are indicated in the treatment of hypertension. Fosinopril Sodium 10mg tablets may be used alone as initial therapy or in combination with other antihypertensive agents. The antihypertensive effects of Fosinopril Sodium 10mg tablets and diuretics used concomitantly are approximately additive.

Heart Failure:
Fosinopril Sodium 10mg tablets are indicated for the treatment of heart failure in combination with a non-potassium sparing diuretic and where appropriate, digitalis. In these patients, Fosinopril Sodium 10mg tablets improve symptoms and exercise tolerance, reduce severity of heart failure and decrease the frequency of hospitalisation for heart failure.

I.7 Dose and Dose Regimen

Method of administration:
Oral

Posology

Hypertensive patients not being treated with diuretics:

The dose range is 10 to 40mg per day administered in a single dose and without regard to meals. The normal starting dose for patients is 10mg once a day. Dosage may need to be adjusted after approximately 4 weeks according to blood pressure response. No additional blood pressure lowering is achieved with doses greater than 40mg daily. If blood pressure is not adequately controlled with Fosinopril Sodium 20mg tablets alone, a diuretic can be added.

Hypertensive patients being treated with concomitant diuretic therapy:

The diuretic should preferably be discontinued for several days prior to beginning therapy with Fosinopril Sodium 20mg tablets to reduce the risk of an excessive hypotensive response. 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 should be used with careful medical supervision for several hours, until blood pressure has stabilised. In diuretic treated hypertensive patients, mean cerebral blood flow is maintained between 4 and 24 hours after fosinopril, despite significant reduction in blood pressure.

Heart Failure:
The recommended initial dose is 10mg once daily, initiated under close medical supervision. If the initial dose is well tolerated patients should then be titrated to a dose of up to 40mg once daily. The appearance of hypotension after the initial dose should not preclude careful dose titration of Fosinopril Sodium 20mg tablets, following effective management of the hypotension. Fosinopril Sodium 20mg tablets should be used in addition to diuretics and digitalis where appropriate.

Heart Failure - High Risk Patients:
It is recommended that treatment is initiated in hospital for patients with severe cardiac failure (NYHA IV) and those at particular risk of first dose hypotension, i.e. patients on multiple or high dose diuretics (e.g.> 80mg furosemide), patients with hypovolaemia, hyponatraemia (serum sodium < 130 meq/l), pre-existing hypotension (systolic blood pressure <90 mmHg), patients with unstable cardiac failure and those on high-dose vasodilator therapy.

CHILDREN

Fosinopril Sodium 20mg tablets should not be used in children under 18 years of age, as benefits have not been established.

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 fosinoprilat have been found compared with younger subjects.

IMPAIRED HEPATIC FUNCTION

Treatment should be initiated at a dose of 10mg. Although the rate of hydrolysis 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 fosinoprilat with compensatory increase in renal excretion.

RENAL IMPAIRMENT

Treatment should be initiated at a dose of 10mg. Depending on the response, the dose should then be titrated to achieve the desired therapeutic effect.

Absorption, bioavailability, protein binding, biotransformation and metabolism are not appreciably altered by reduced renal function. In patients with impaired renal function, the total body clearance of fosinoprilat is approximately 50% slower than that in patients with normal renal function. However, since hepatobiliary elimination compensates at least partially for diminished renal elimination, the body clearance of fosinoprilat is not appreciably different over a wide range of renal insufficiency (creatinine clearances ranging from <10 to 80 ml/min/1.73m2, i.e. including end-stage renal failure).

Neither haemodialysis nor peritoneal dialysis is effective in clearing fosinoprilat. Peritoneal clearance is insignificant, ranging from 0.07 to 0.23ml per minute. Similarly haemodialysis for four hours clears only approximately 1.5% of the administered dose. This corresponds to 7% and 2% respectively, of urea clearance. Hence no dose adjustment is necessary to correct for drug loss during these procedures.

NB Fosinopril is NOT licensed for use in acute myocardial infarction.

I.8 Consideration for Paediatric use

The brand leader Staril is authorised for use in children older than 12 years. There are no specific data to support the safety of fosinopril in children of any age (<12 years or 12-18 year olds). The current generic application does not provide any new data for such use and has no paediatric development programme.

I.9 Assessor's Comments

The current SPC in line with other ACE inhibitors (such as Lisinopril, Enalapril, Perindopril, or Quinapril) proscribes use in children, while Staril the reference product is authorised for those above 12 years of age.

The EC directive 75/318/EEC, guidance note on clinical investigation of medicinal products in children, states "for legal purposes, the upper age of consent for regulatory purposes will depend on the age of personal consent". In view of this, it is considered best to recommend fosinopril use only in those over the age of 18.

I. CLINICAL PHARMACOLOGY

No Pharmacokinetics data were presented or were required for this type of application.

II.2 Pharmacodynamics

No Pharmacodynamic data were presented or were required for this type of application.

III.1 Bioequivalence studies

The applicant has provided two bioavailability / bioequivalence studies in support of this application. The first Study compared 10mg of Delta fosinopril and 10mg Fosinorm (Germany) while the second study compared 20mg strength of Delta fosinopril with 20 mg Staril, (ER Squibb /BMS, UK). The final reports were generated in October 2002. The study complied with GCP guidelines.

These were randomised, 2-way crossover, single-dose, two-treatment, two-period study that included 32 healthy, non-smoker, subjects (age 18-55 years). During each period, 17 plasma samples were taken at specified intervals from each subject extending between pre-dose to 48 hours post-dose. Fosinoprilat was measured in the plasma using a validated LC/MS/MS method, complying with the GLP guidelines.

The summary of the results are shown in the following tables:

1. Bioequivalence study-

Test Prod: Fosinopril 10 mg
Reference Product: Fosinorm Sodium 10 mg, Wirkstoff

Fosinoprilat pharmacokinetics:

Parameter	Test (mean)	Fosinorm (B)	GM Ratio(90% CI)
Cmax (ng/ml)	147.6	148.2	99.6 (93.1-106.6)
AUC 0-t (ng*hr/ml)	1068.03	1052.41	101.5 (94.8-108.7)
AUC 0-inf (ng*hr/ml)	1121.57	1109.79	101.1 (94.6-107.0)
Tmax	3.9	3.8	

Data from CTD modl-5 of applicant's dossier

2. Bioequivalence study-

Test Prod: Fosinopril 20 mg
Reference Product: Staril™ ER Squibb/ BMS 20mg tablets

Fosinoprilat pharmacokinetics:

Parameter	Test (mean)	Staril (B)	GM Ratio(90% CI)
Cmax (ng/ml)	319.4	294.0	108.6 (103.5-113.9)
AUC 0-t (ng*hr/ml)	2274.33	2083.08	109.2 (104.5-114.1)
AUC 0-inf (ng*hr/ml)	2345.19	2138.4	109.7 (104.9-114.7)
Tmax	3.4	3.5	

Data from CTD module-5 of applicant's dossier

The products were shown to be bioequivalent at both strengths, albeit with a marginally higher AUC and C_{max} for the test product. The results are within the prescribed range 80-125%. The CPMP criteria are therefore satisfied for bioequivalence.

Bioequivalence: From the result of the two studies it is accepted that equivalence has been demonstrated between the two products.

IV CLINICAL EFFICACY

No new data has been provided.

V. CLINICAL SAFETY

No new safety issues were noted during the bioequivalence studies.

VI. CLINICAL EXPERT REPORT

A clinical expert report has been written by a suitably qualified person and is satisfactory.

VII. PRODUCT LITERATURE

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is consistent with that for the reference product and is satisfactory.

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

LABELLING
This is satisfactory

APPLICATION FORMS (MAA)
This is satisfactory.

MEDICAL CONCLUSION
The bioequivalence study submitted has shown that this product can be considered as generic medicinal product to the originator product Staril Tablets (ER Squibb & Sons).

Marketing authorisation is recommended for this application.

Overall Conclusion

Quality
The quality aspects of Fosinopril sodium are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Pre-Clinical
No new pre-clinical data were presented or were required for this type of application.

Clinical
No new data were submitted and none are required for applications of this type. Bioequivalence between this product and the reference product has been demonstrated. The reference product used in the bioequivalence study is representative of the originator product marketed in the UK.

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

Benefit/Risk Analysis
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Fosinopril sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
07/03/2007	Type II	To update SPC Sections 4.4 “Special warnings and precautions for use”, 5.1”Pharmacodynamic properties” and 5.2”Pharmacokinetic properties” and the PIL (UK licence) following finalisation of MRP procedure UK/H/910/01/MR.	Approved 16/07/2007
15/05/2007	Type 1A	To change MA holder	Approved 18/05/2007