Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zestril 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains lisinopril 5 mg (as dihydrate).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

Product sourced in Spain:
Pink, round, biconvex, uncoated tablets with '5' on one side and a breakline on the other.

Product sourced in France:
Pink, round, biconvex, uncoated tablets, impressed with a heart shape and '5' on one side and a breakline on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension: Zestril is indicated in the treatment of essential hypertension and in renovascular hypertension. It may be used alone or concomitantly with other classes of antihypertensive agents.

Congestive Heart Failure: Zestril is indicated in the management of congestive heart failure as an adjunctive treatment with diuretics and, where appropriate, digitalis. High doses reduce the risk of combined outcomes of mortality and hospitalization *(see dosage and administration)* but may also predispose to adverse effects *(see section ''Undesirable effects'').*

Acute Myocardial Infarction: Zestril is indicated for the treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction, to prevent the subsequent development of left ventricular dysfunction or heart failure and to improve survival.

Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blocker.

Diabetes Mellitus patients with nephropathy: In normotensive insulin-dependent and hypertensive type 2 diabetes mellitus patients who have incipient nephropathy characterised by microalbuminuria, (>20µg/min or 30mg/day of microalbumin which has not responded to dietary measures and improved metabolic control). Zestril may be considered for use in these patients after appropriate advice regarding diet and metabolic control is given. Zestril reduces urinary albumin excretion rate.

4.2 Posology and method of administration

Since absorption of Zestril tablets is not affected by food, the tablets may be administered before, during or after meals. Zestril should be administered in a single daily dose. As with all other medication taken once daily, Zestril should be taken at approximately the same time each day.

Hypertension: The need for dosage titration should be determined by measurement of the blood pressure just before the next dose.

Essential Hypertension: In patients with essential hypertension the usual recommended starting dose is 10mg. The usual effective maintenance dosage is 20mg administered in a single daily dose. Dosage should be adjusted according to blood pressure response. In general, if the desired therapeutic effect cannot be achieved in a period of 2 to 4 weeks on a certain dose level, the dose can be further increased. The maximum dose used in long-term, controlled clinical trials was 80mg daily. A lower starting dose is required in the presence of renal impairment, in patients in whom diuretic therapy cannot be discontinued, patients who are volume and/or salt depleted for any reason, and in patients with renovascular hypertension.

Diuretic Treated Patients: Symptomatic hypotension may occur following initiation of therapy with Zestril; this is more likely in patients who are being treated currently with diuretics. Caution is recommended, therefore, since these patients may be volume and or salt-depleted. If possible the diuretic should be discontinued or the dose reduced 2 to 3 days before beginning therapy with Zestril (see 'Special warnings and special precautions for use'). In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Zestril should be initiated with a 5mg dose. The subsequent dosage of Zestril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed.

Dosage Adjustment in Renal Impairment: Dosage in patients with renal impairment should be based on creatinine clearance as outlined in *Table 1.*

Table 1

Creatinine Clearance (ml/min)	**Starting Dose (mg/day)**
less than 10ml/min (including patients on dialysis)	2.5mg *
10-30 ml/min	2.5 – 5mg
31-70 ml/min	5 – 10mg

* Dosage and/or frequency of administration should be adjusted depending on the blood pressure response.

The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40mg daily.

Renovascular Hypertension: Some patients with renovascular hypertension, especially those with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, may develop an exaggerated response to the first dose of Zestril. Therefore, a lower starting dose of 2.5 or 5mg is recommended. Thereafter, the dosage may be adjusted according to the blood pressure response.

Congestive Heart Failure: As adjunctive therapy with diuretics and, where appropriate, digitalis, Zestril may be initiated with a dose of 2.5mg once a day. The dose of Zestril should be increased:

- By increments of no greater than 5-10mg
- at intervals of no less than 2 weeks
- to the highest dose tolerated by the patient up to a maximum of 35mg once daily.

Dose adjustment should be based on the clinical response of individual patients.

Patients at high risk of symptomatic hypotension e.g. patients with salt depletion with or without hyponatraemia, patients with hypovolaemia or patients who have been receiving vigorous diuretic therapy, should have these conditions corrected, if possible, prior to therapy with Zestril. The effect of the starting dose of Zestril on blood pressure should be monitored carefully. Serum potassium and renal function should also be monitored regularly.

Acute Myocardial Infarction: Treatment with Zestril may be started within 24 hours of the onset of symptoms. The first dose of Zestril is 5mg given orally, followed by 5mg after 24 hours, 10mg after 48 hours and then 10mg once daily

thereafter. Patients with a low systolic blood pressure (120 mmHg or less) when treatment is started or during the first 3 days after the infarct should be given a lower dose — 2.5mg orally *(see ‘‘Special warnings and special precautions for use’’).* If hypotension occurs (systolic blood pressure less than, or equal to, 100 mmHg) a daily maintenance dose of 5mg may be given with temporary reductions to 2.5mg if needed.

If prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour) Zestril should be withdrawn.

Dosing should continue for six weeks. Patients who develop symptoms of heart failure should continue with Zestril. *(See ‘‘Posology and method of administration’’ for Congestive Heart Failure).*

Zestril is compatible with intravenous or transdermal glyceryl trinitrate.

Renal Complications of Diabetes Mellitus: In normotensive, insulin-dependent diabetes mellitus patients with microalbuminuria, (>20micrograms/min or 30mg/day of microalbumin which has not responded to dietary measures and improved metabolic control). A dose of 2.5-10mg Zestril once daily which can be increased to 20mg once daily if necessary, to achieve a reduction to <20micrograms/min or <30mg/day of microalbumin. Advice regarding dietary protein and metabolic control should also be given. In hypertensive type 2 diabetes mellitus patients, the dose schedule is as above aiming to achieve a sitting blood pressure ≤130/80mmHg.

Paediatric Use: Safety and effectiveness of Zestril in children has not been established.

Use in the Elderly: When advanced age is associated with decrease in renal function, the guidelines set out in Table 1 should be used to determine the starting dose of Zestril. Thereafter, the dosage should be adjusted according to the blood pressure response.

4.3 Contraindications

Zestril is contra-indicated in patients who are hypersensitive to any component of this product and in patients with a history of angioneurotic oedema relating to previous treatment with an angiotensin-converting enzyme inhibitor and in patients with hereditary or idiopathic angioedema.

The use of lisinopril during pregnancy is contra-indicated. When pregnancy is detected, lisinopril should be discontinued as soon as possible unless it is considered life-saving for the mother.

Use in patients with cor pulmonale or outflow tract obstruction.

Lisinopril products should not be used in women of childbearing potential unless protected by effective contraception.

See also ‘‘Use in Pregnancy’’ and ‘‘Nursing Mothers’’.

4.4 Special warnings and precautions for use

Symptomatic Hypotension: Symptomatic hypotension was seen rarely in uncomplicated hypertensive patients. In hypertensive patients receiving Zestril hypotension is more likely to occur if the patient has been volume-depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting *(see ‘‘Undesirable effects’’).* In patients with congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment.

In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be monitored under close medical supervision. Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contra-indication to further treatment.

As with other vasodilators, Zestril should be given with caution to patients with aortic stenosis or hypertrophic cardiomyopathy.

In some patients with congestive heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with Zestril. This effect is anticipated and is not usually a reason to discontinue treatment. Such patients should be kept under close medical supervision. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Zestril may be necessary.

Hypotension in Acute Myocardial Infarction: Treatment with lisinopril must not be initiated in acute myocardial infarction patients who are at risk of further serious haemodynamic deterioration after treatment with a vasodilator. These are patients with systolic blood pressure of 100mmHg or lower or cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120mmHg or lower. Maintenance doses should be reduced to 5mg or temporarily to 2.5mg if systolic blood pressure is 100mmHg or lower. If hypotension persists (systolic blood pressure less than 90mmHg for more than 1 hour) then Zestril should be withdrawn.

Renal Function Impairment: Assessment of renal function: Evaluation of the patient should include assessment of renal function prior to initiation of therapy and during treatment.

Impaired renal function: Zestril should be used with caution in patients with renal insufficiency, as they may require reduced or less frequent doses *(see ''Dosage and Administration'').* Close monitoring of renal function during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter, or may improve.

Renal failure has been reported in association with ACE inhibitors and has been mainly in patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis. If recognized promptly and treated appropriately, renal failure is usually reversible.

Zestril can be used when surgery is not indicated or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases of blood urea and serum creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypotension is present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of Zestril therapy.

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

In acute myocardial infarction, treatment with lisinopril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500mg/24h. If renal dysfunction develops during treatment with Zestril (serum creatinine concentration exceeding 265 micromol/l or a doubling from the pre-treatment value) then the physician should consider withdrawal of Zestril.

Haemodialysis Patients: Anaphylactoid reactions have been reported in patients undergoing certain haemodialysis procedures (e.g. with the high flux membrane AN 69) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or different class of antihypertensive agent. Zestril is not recommended in patients on haemodialysis.

Hypersensitivity/Angioneurotic Oedema: Angioneurotic Oedema has been reported rarely with ACE inhibitors, including Zestril. In some cases symptoms have been observed up to 2 years after initiation of treatment. Such reactions should be regarded as an indication to discontinue therapy immediately and the patient closely monitored.

Where swelling is confined to the face, lips and mouth, the condition will usually resolve without further treatment, although antihistamines may be useful in relieving symptoms.

These patients should be followed carefully until the swelling has resolved. However, where there is involvement of the tongue, glottis or larynx, likely to cause airways obstruction, appropriate therapy, should be administered promptly. This may include the administration of subcutaneous adrenaline (0.5 ml 1:1000) 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.

Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Patients with a history or angioeodema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor *(See also ‘‘Contraindications’’).*

Other hypersensitivity reactions have been reported.

Desensitisation: Patients receiving ACE inhibitors during 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 rechallenge.

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.

Surgery/Anaesthesia: In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Zestril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

General: Since there is little experience in the treatment of aortic stenosis, cor pulmonale or outflow tract obstruction, the use of Zestril is not recommended in these conditions.

Where Zestril is used as a single agent in hypertension, Afro Caribbean patients may show a reduced therapeutic response.

Race: Angiotensin converting enzyme inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with other antihypertensive agents such as beta blockers, calcium antagonists, methyldopa and diuretics may increase the antihypertensive efficacy. Zestril minimises the development of thiazide-induced hypokalemia and hyperuricaemia. Indomethacin may reduce the antihypertensive efficacy of Zestril. In some patients with compromised renal function who are being treated with non-steriodal anti-inflammatory drugs (NSAIDS), the co-administration of lisinopril may result in a further deterioration in renal function.

As Zestril may reduce the elimination of lithium, serum levels of lithium should be monitored if lithium salts are administered.

Concomitant administration of ACE inhibitors and anti-diabetic medicines (insulin, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with the risk of hypoglycaemia. The phenomenon may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Serum Potassium: Usually remains within normal limits. If Zestril is given with a diuretic, the likelihood of diuretic induced hypokalemia may be lessened. Zestril may elevate plasma potassium levels in patients with renal failure.

Potassium supplements, potassium sparing diuretics and potassium containing salt substitutes are not recommended.

4.6 Pregnancy and lactation

Use in Pregnancy: The use of lisinopril during pregnancy is contra-indicated. When pregnancy is detected, lisinopril should be discontinued as soon as possible unless it is considered life saving for the mother.

Zestril has been shown to be foetotoxic in rabbits during middle and late pregnancy. Effects of exposure of the foetus to ACE inhibitors during the first trimester of human pregnancy are unknown. Foetal exposure during the second and third trimesters of pregnancy has been associated with foetal and neonatal morbidity and mortality.

If lisinopril is used during pregnancy, the patient should be informed of the potential hazard to the foetus. ACE inhibitors in human pregnancy have been associated with oligohydramnios. Hypertension and renal failure have occurred in the new born. Because of these findings, Zestril is contra-indicated in pregnancy.

Infants whose mothers have taken lisinopril should be closely observed for hypotension, oliguria and hyperkalemia.

Breast Feeding Mothers: It is not known whether Zestril is excreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if Zestril is to be given to women who are breast feeding.

4.7 Effects on ability to drive and use machines

No specific precautions but see *''Undesirable effects''*.

4.8 Undesirable effects

Zestril has been found in controlled clinical trials to be generally well tolerated. For the most part, side effects were mild and transient in nature.

Hypotension has occurred in association with therapy with Zestril. This appears to occur in certain specific sub-groups *(see ''Special warnings and special precautions for use'').*

The most frequent clinical side effects of Zestril in controlled trials were: dizziness, headache, diarrhoea, fatigue, cough and nausea. Other side effects occurring less frequently were: orthostatic effects (including hypotension), rash and asthenia. In patients with congestive heart failure, high doses of Zestril may predispose to symptoms related to hypotension (dizziness, syncope) and to biochemical changes related to impaired renal function (hyperkalaemia and increased serum creatinine) as would be expected with ACE inhibitor therapy.

Hypersensitivity/Angioneurotic Oedema: Angioneurotic oedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely *(see ''Special warnings and precautions for use'').*

Side-effects which occurred rarely, either during controlled clinical trials or after the drug was marketed, include:

Cardiovascular: Myocardial infarction or cerebrovascular accident possibly secondary to excessive hypotension in high risk patients *(see ''Special warnings and special precautions for use'')* palpitations, tachycardia.

Digestive: Abdominal pain and indigestion, dry mouth, hepatitis (hepatocellular or cholestatic), jaundice, pancreatitis, vomiting.

Nervous System: Mood alterations, mental confusion, paraesthesia, vertigo, as with other angiotensin converting enzyme inhibitors, taste disturbances and sleep disturbances have been reported.

Respiratory: Bronchospasm, rhinitis, sinusitis.

Skin: Alopecia, urticaria, diaphoresis, pruritis, psoriasis and severe skin disorders have been reported including pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme.

Urogenital: uraemia, oliguria/anuria, renal dysfunction, acute renal failure, impotence A symptom complex has been reported which may include one or more of the following:— fever, vasculitis, myalgia, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia and leukocytosis, rash, photosensitivity or other dermatological manifestations.

Laboratory Test Findings: Clinically important changes in standard laboratory parameters were rarely associated with administration of Zestril. Increases in blood urea, serum creatinine, liver enzymes and serum bilirubin, usually reversible upon discontinuation of Zestril, have been seen.

Bone marrow depression manifest as anaemia, and/or thrombocytopenia and / or leucopenia has been reported. Agranulocytosis has been rarely reported although a causal relationship has not been established. Rarely, haemolytic anaemia has been reported.

Small decreases in haemoglobin and haematocrit, rarely of clinical importance unless another cause of anaemia coexisted, have occurred.

Leucopenia and thrombocytopenia have also been reported; a causal relationship to therapy with Zestril has not been established.

Hyperkalemia has occurred.

Hyponatraemia has occurred.

4.9 Overdose

The symptoms of overdose may include sever 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 should be given rapidly. Treatment with angiotensin II (if available) may be considered. Angiotensin converting enzyme inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile dialysis membranes should be avoided. Serum electrolytes and creatinine should be monitored frequently.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II which results in decreased vasopressor activity and reduced aldosterone secretion.

The latter decrease may result in an increase in serum potassium concentration.

While the mechanism through which lisinopril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, lisinopril is antihypertensive even in patients with low-renin hypertension.

ACE is identical to kininase II, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodilatory peptide, play a role in the therapeutic effects of lisinopril remains to be elucidated.

A previous study has indicated that Lisinopril in dose ranging from 2.5-10mg over a 3 month period has improved NYHA classification and exercise tolerance in patients with moderate to severe congestive cardiac failure.

More recently the effect of Zestril on mortality and morbidity in congestive heart failure has been studied by comparing a high dose (32.5 mg or 35 mg once daily) with a low dose (2.5 mg or 5 mg once daily). In a study of 3164 patients, with a median follow up period of 46 months for surviving patients, high dose Zestril produced a 12% risk reduction in

the combined endpoint of all-cause mortality and all-cause hospitalisation (p = 0.002) and an 8% risk reduction in all-cause mortality and cardiovascular hospitalisation (p = 0.036) compared with low dose. Risk reductions for all-cause mortality (8%; p = 0.128) and cardiovascular mortality (10%; p = 0.073) were observed. In a post-hoc analysis, the number of hospitalisations for heart failure was reduced by 24% (p=0.002) in patients treated with high-dose Zestril compared with low dose. Symptomatic benefits were similar in patients treated with high and low doses of Zestril.

The results of the study showed that the overall adverse event profiles for patients treated with high or low dose Zestril were similar in both nature and number. Predictable events resulting from ACE inhibition, such as hypotension or altered renal function, were manageable and rarely led to treatment withdrawal. Cough was less frequent in patients treated with high dose Zestril compared with low dose.

ACE is known to be present in the endothelium and increased ACE activity results in the formation of angiotensin II and destruction of bradykinin. Angiotensin II has been implicated in the pathogenesis of the damage to the endothelium associated with diabetes mellitus. ACE inhibitors, including lisinopril, inhibit the formation of angiotensin II and breakdown of bradykinin and hence ameliorate endothelial dysfunction.

In normotensive IDDM patients and in hypertensive type 2 diabetic patients treatment with lisinopril resulted in a reduction of the urinary albumin excretion rate.

In a small number of normotensive IDDM patients with retinopathy a beneficial effect of lisinopril on the progression of the retinopathy was seen. The mechanism of this remains to be further explored.

While lisinopril treatment is not associated with an increased incidence of hypoglycaemic events in diabetic patients the use of angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides.

5.2 Pharmacokinetic properties

Following oral administration of lisinopril, peak serum concentrations occur within about 7 hours, although there was a trend to a small delay in time taken to reach peak serum concentrations in acute myocardial infarction patients. On multiple dosing lisinopril has an effective half life of accumulation of 12.6 hours.

Declining serum concentrations exhibit a prolonged terminal phase which does not contribute to drug accumulation. This terminal phase probably represents saturable binding to ACE and is not proportional to dose. Lisinopril does not appear to bind to other serum proteins.

Impaired renal function decreases elimination of lisinopril, which is excreted via the kidneys, but this decrease becomes clinically important only when the glomerular filtration rate is below 30 ml/min. Older patients have higher blood levels and higher values for the area under the plasma concentration time curve than younger patients. Lisinopril can be removed by dialysis.

Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25%, with interpatient variability (6-60%) at all doses tested (5-80mg).

Lisinopril does not undergo metabolism and absorbed drug is excreted unchanged entirely in the urine. Lisinopril absorption is not affected by the presence of food in the gastrointestinal tract.

Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Angiotensin converting enzyme inhibitors may have a lesser effect on blood pressure in black hypertensive patients than in non-black hypertensive patients.

When combined with other antihypertensive agents, additive falls in blood pressure may occur.

5.3 Preclinical safety data

No other relevant information other than that provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Magnesium stearate
Maize starch
Pregelatinised maize starch
Red iron oxide (E172)
Mannitol

6.2 Incompatibilities

None known.

6.3 Shelf Life

The shelf life expiry date for this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Al/PVC blister. Packs of 28 and 60.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special instructions.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PRIMECROWN Ltd
28 Sarum Complex
Uxbridge
Middlesex UB8 2RZ
England

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1071/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 December 2002