ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Vienna Austria	Acemin	2.5 mg	Tablet	Oral use	Aluminium/PVC blister	28
Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Vienna Austria	Acemin	5 mg	Tablet	Oral use	Aluminium/PVC blister	28
Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Vienna Austria	Acemin	10 mg	Tablet	Oral use	Aluminium/PVC blister	28
Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Vienna Austria	Acemin	20 mg	Tablet	Oral use	Aluminium/PVC blister	28
Austria	AstraZeneca Österreich GmbH Schwarzenbergplatz 7 A-1037 Vienna	Acemin	30 mg	Tablet	Oral use	Aluminium/PVC blister	28

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
	Austria						
Belgium	NV Astra-Zeneca SA Rue Egide Van Ophem straat,110 B-1180 Brussels Belgium	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	28/56
Belgium	NV Astra-Zeneca SA Rue Egide Van Ophem straat,110 B-1180 Brussels Belgium	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	28
Belgium	NV Astra-Zeneca SA Rue Egide Van Ophem straat,110 B-1180 Brussels Belgium	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28/56
Belgium	NV Astra-Zeneca SA Rue Egide Van Ophem straat,110 B-1180 Brussels Belgium	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	28
Denmark	AstraZeneca A/S Roskildevej 22 DK - 2620	Zestril	2.5 mg	Tablet	Oral use	Aluminium/PVC blister	14

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
	Albertslund Denmark						
Denmark	AstraZeneca A/S Roskildevej 22 DK - 2620 Albertslund Denmark	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	28/98
Denmark	AstraZeneca A/S Roskildevej 22 DK - 2620 Albertslund Denmark	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	28/98
Denmark	AstraZeneca A/S Roskildevej 22 DK - 2620 Albertslund Denmark	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28/98
Denmark	AstraZeneca A/S Roskildevej 22 DK - 2620 Albertslund Denmark	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	
Finland	AstraZeneca Oy Luomanportti 3	Zestril	2.5 mg	Tablet	Oral use	Aluminium/PVC blister	14

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
	FIN-02200 Espoo Finland						
Finland	AstraZeneca Oy Luomanportti 3 FIN-02200 Espoo Finland	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	28/98
Finland	AstraZeneca Oy Luomanportti 3 FIN-02200 Espoo Finland	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28/98
Finland	AstraZeneca Oy Luomanportti 3 FIN-02200 Espoo Finland	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	28/98
France	AstraZeneca 1, place Renault 92844 Rueil Malmaison France	Zestril	5 mg	Tablet	Oral	Aluminium/PVC blister	28/100
France	AstraZeneca 1, place Renault 92844 Rueil Malmaison France	Zestril	20 mg	Tablet	Oral	Aluminium/PVC blister	28/100

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Germany	AstraZeneca GmbH Tinsdaler Weg 183 22880 Wedel Germany	Acerbon Aceday Listen	2.5 mg	Tablet	Oral use	Aluminium/PVC blister	30/40/50/100 samples : 20 hospital : 400
Germany	AstraZeneca GmbH Tinsdaler Weg 183 22880 Wedel Germany	Acerbon Aceday Listen	5 mg	Tablet	Oral use	Aluminium/PVC blister	30/40/50/100 samples : 20 hospital : 400
Germany	AstraZeneca GmbH Tinsdaler Weg 183 22880 Wedel Germany	Acerbon Aceday Listen	10 mg	Tablet	Oral use	Aluminium/PVC blister	30/40/50/100 samples : 20 hospital : 400
Germany	AstraZeneca GmbH Tinsdaler Weg 183 22880 Wedel Germany	Acerbon Aceday Listen	20 mg	Tablet	Oral use	Aluminium/PVC blister	30/40/50/100 samples : 20 hospital : 400
Greece	Pharmaceutical Laboratories 446 Irakliou Avenue 141 22 Iraklio CANA SA Athens	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	14/28

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
	Greece						
Greece	Pharmaceutical Laboratories 446 Irakliou Avenue 141 22 Iraklio CANA SA Athens Greece	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	14
Greece	Pharmaceutical Laboratories 446 Irakliou Avenue 141 22 Iraklio CANA SA Athens Greece	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	14
Greece	Pharmaceutical Laboratories 446 Irakliou Avenue 141 22 Iraklio CANA SA Athens Greece	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	14
Greece	Pharmaceutical Laboratories 446 Irakliou Avenue 141 22 Iraklio CANA SA Athens Greece	Zestril	40 mg	Tablet	Oral use	Aluminium/PVC blister	

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU	Zestril	2.5 mg	Tablet	Oral use	Aluminium/PVC blister	28
Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	28
Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	28
Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28
Ireland	AstraZeneca UK Ltd 600 Capability Green Luton LU1 3LU	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Italy	AstraZeneca SPA Via F Sforza - Palazzo Volta, 20080 Basiglio (MI)	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	14
Italy	AstraZeneca SPA Via F Sforza - Palazzo Volta, 20080 Basiglio (MI)	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	14
Italy	AstraZeneca SPA Via F Sforza - Palazzo Volta, 20080 Basiglio (MI)	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	14
Italy	AstraZeneca SPA Via F Sforza - Palazzo Volta, 20080 Basiglio (MI)	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Luxembourg	NV AstraZeneca SA , rue Egide Van Ophem straat ,110 B-1180 Brussels Belgium	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	28/56
Luxembourg	NV AstraZeneca SA , rue Egide Van Ophem straat ,110 B-1180 Brussels Belgium	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28/56
Netherlands	AstraZenca BV Postbus 599 2700 An Zoetermeer Netherlands	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister and Aluminium PVC/PVDC blister HDPE	30 EAV hospital pack: 50 30

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Netherlands	AstraZenca BV Postbus 599 2700 An Zoetermeer Netherlands	Zestril	10	Tablet	Oral use	Aluminium/PVC blister and Aluminium PVC/PVDC blister HDPE	30 EAV hospital pack: 50 30
Netherlands	AstraZenca BV Postbus 599 2700 An Zoetermeer Netherlands	Zestril	20	Tablet	Oral use	Aluminium/PVC blister and Aluminium PVC/PVDC blister HDPE	30 EAV hospital pack: 50 30

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Netherlands	AstraZenca BV Postbus 599 2700 An Zoetermeer Netherlands	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister HDPE	30 EAV hospital pack: 50 30
Netherlands	AstraZenca BV Postbus 599 2700 An Zoetermeer Netherlands	Zestril	40 mg	Tablet	Oral use		
Norway	AstraZeneca AS Postboks 200 Vinderen N-0319 Oslo Norway	Zestril	2.5 mg	Tablet	Oral use	Aluminium/PVC blister	14/100
Norway	AstraZeneca AS Postboks 200 Vinderen N-0319 Oslo Norway	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	28/98/100

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Norway	AstraZeneca AS Postboks 200 Vinderen N-0319 Oslo Norway	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	28/98/100
Norway	AstraZeneca AS Postboks 200 Vinderen N-0319 Oslo Norway	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28/98/100
Norway	AstraZeneca AS Postboks 200 Vinderen N-0319 Oslo Norway	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	
Portugal	AstraZeneca Produtos Farmacêuticos, Lda Rua Humberto Madeira, 7 Valejas 2745-663 Barcarena Portugal	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	14/28/56

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Portugal	AstraZeneca Produtos Farmacêuticos, Lda Rua Humberto Madeira, 7 Valejas 2745-663 Barcarena Portugal	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	28/56
Portugal	AstraZeneca Produtos Farmacêuticos, Lda Rua Humberto Madeira, 7 Valejas 2745-663 Barcarena Portugal	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28/56
Portugal	AstraZeneca Produtos Farmacêuticos, Lda Rua Humberto Madeira, 7 Valejas 2745-663 Barcarena Portugal	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	
Spain	AstraZeneca Farmaceutica Spain SA C/Serrano Galvache 56 Edificio Roble ES 28033 Madrid Spain	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	60/500

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Spain	AstraZeneca Farmaceutica Spain SA C/Serrano Galvache 56 Edificio Roble ES 28033 Madrid Spain	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28/500
Spain	AstraZeneca Farmaceutica Spain SA C/Serrano Galvache 56 Edificio Roble ES 28033 Madrid Spain	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	
Sweden	Hässle Läkemedel AB S-431 86 Mölndal Sweden	Zestril	2.5 mg	Tablet	Oral use	Aluminium/PVC blister	14
Sweden	Sweden Hässle Läkemedel AB S-431 86 Mölndal	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	28/98/100

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Sweden	Sweden Hässle Läkemedel AB S-431 86 Mölndal	Zestril	5 mg	Tablet	Oral use	Polypropylene tube	100
Sweden	Sweden Hässle Läkemedel AB S-431 86 Mölndal	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	28/98/100
Sweden	Sweden Hässle Läkemedel AB S-431 86 Mölndal	Zestril	10 mg	Tablet	Oral use	Polypropylene tube	100
Sweden	Sweden Hässle Läkemedel AB S-431 86 Mölndal	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28/98/100

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
Sweden	Sweden Hässle Läkemedel AB S-431 86 Mölndal	Zestril	20 mg	Tablet	Oral use	Polypropylene tube	100
Sweden	Sweden Hässle Läkemedel AB S-431 86 Mölndal	Zestril	30 mg	Tablet	Oral use	Aluminium/PVC blister	28/98/100
UK	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU	Zestril	2.5 mg	Tablet	Oral use	Aluminium/PVC blister	28
UK	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU	Zestril	5 mg	Tablet	Oral use	Aluminium/PVC blister	28

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration	Packaging	Package size
UK	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU	Zestril	10 mg	Tablet	Oral use	Aluminium/PVC blister	28
UK	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU	Zestril	20 mg	Tablet	Oral use	Aluminium/PVC blister	28
UK	AstraZeneca UK Limited 600 Capability Green Luton Bedfordshire LU1 3LU	Zestril	30	Tablet	Oral use		

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ZESTRIL AND ASSOCIATED NAMES (see Annex I)

Quality issues

No significant issues relating to Quality were identified.

The pharmaceutical particulars of the SPC were harmonised, except the sections, which need to be introduced nationally by the Member States when implementing the harmonised SPC (section 6).

Efficacy issues

The divergences that previously existed across the SPCs of EU Member States included:

Section 4.1 Therapeutic Indications

The MAH was requested to propose and scientifically justify a common EU wide approach as there were divergences between national approvals regarding the use of Zestril in:

- The treatment of hypertension (arterial hypertension and renovascular hypertension) and its use alone or in association with thiazides diuretics.
- And the treatment of incipient nephropathy in diabetics characterised by microalbuminuria (30-300 mg/24h), this indication was not approved in all the EU member states.

Hypertension

Multiple publications, referred to in the response document, and long-standing clinical experience support the unrestricted indication.

Acute Myocardial Infarction

Consensus treatment guidelines identify ACEi as established therapy in the setting of acute myocardial infarction. The pivotal lisinopril-specific data emanate from GISSI-3, which identified lasting outcome benefit from six weeks of lisinopril therapy, when started within 24h after AMI in haemodynamically stable patients. Objectives of therapy are stated in the pharmacodynamic section of the summary of product characteristics.

Heart Failure

Treatment of symptomatic HF is considered evidence-based therapy for ACEi as a class. For lisinopril, adequate substance-specific outcome data emanate mainly from the ATLAS trial. Since the objectives with treatment of symptomatic HF with ACEi are well described in standard medical text books and the outcome information from ATLAS is given in section 5.1 of the summary of product characteristics for Zestril.

Renal complications of diabetes mellitus

The indications proposed in relation to incipient nephropathy are specific to lisinopril, as compared with other ACE inhibitors (ACEi), and will be scrutinised in some detail:

Substance-specific documentation of the effect of lisinopril on renal and retinal complications of diabetes mellitus emanates from two trials: study 306 (EUCLID) performed in normotensive IDDM patients and study 298 (BRILLIANT) in hypertensive NIDDM patients.

Incipient nephropathy in normotensive IDDM patients (study 306)
EUCLID was a European multicentre randomised trial of lisinopril (n=265) and placebo (n=265) in IDDM patients with "normotension", defined as DBP 75-90 mmHg and SBP ≤155 mmHg, aged 20-59 years, with <36 years of age at onset of IDDM and need for insulin therapy within 12 months of diagnosis.

After a 1-month placebo run-in period, lisinopril 2.5 mg or placebo was given at randomisation followed by lisinopril 10 mg od or placebo od. The dose was doubled if DBP >75 mmHg at any time after 3 months. Duration of the trial was 24 months. Nifedipine 20 mg twice daily (bd) in an open manner was allowed if SBP > 160 mmHg or DBP > 95 mmHg on 2 consecutive occasions within a 4-week period at any time during the trial.

The primary efficacy endpoint was the rate of change in urinary albumin excretion rate (AER) at 24 months. Secondary endpoints were glomerular filtration rate (GFR), retinopathy, vascular risk factors (lipid and haemostatic factors), glycosylated haemoglobin (HbA_{1C}), BP, heart rate, and quality of life.

At baseline, the included patients, with a mean age of 34 years and a mean duration of IDDM of 14-15 years, had a mean AER of 8 ug/min. Only 13 % of patients with placebo and 17% with lisinopril had evidence of microalbuminuria (AER 20-200 µg/min), although 40% had been assumed for the calculation of the statistical power of the trial. Mean SBP was 122±11 and 123±11 mmHg, and mean DBP was 80±5 and 80±4 mmHg in the lisinopril and placebo groups, respectively.

Primary efficacy outcomes
Lisinopril produced a 2.2 µg/min lower mean AER compared with placebo (p=0.03) after 24 months of treatment and after adjustment for baseline AER and trial centre, as specified in the protocol (Table 1). When adjusted for BP, the difference was reduced to 17.3% (p=0.05).

Table 1 Urinary AER at baseline and at the end of 24 months of treatment

Treatment	Baseline			24 months		
	n	Geometric mean	25th, 75th percentile	n	Geometric mean	25th, 75th percentile
Lisinopril	262	8.0	4.4, 14.8	230	7.4	4.4, 10.7
Placebo	263	8.0	4.7, 14.0	226	9.5	4.5, 15.2

The effect of lisinopril and placebo was further compared in patients who were normo-albuminuric (AER<20 µg/min) or microalbuminuric (AER 20-200 µg/min) at baseline (Table 2). No significant difference between the treatment groups was found in the relative % difference in AER although there was a tendency in favour of lisinopril.

Table 2 Group-difference in AER decrease at 24 months (lisinopril - placebo) and in relative % difference in AER (which is the % by which AER is lower in lisinopril compared with placebo group) in patients with normoalbuminuria or microalbuminuria at baseline

At baseline	Group-difference in AER decrease			
	µg /min	%	95% CI	p =
Normoalbuminuric	1.0	12.7	-2.9; 26	0.1
Microalbuminuric*	34.2	49.7	-14.5; 77.9	0.1

* n=39 in lisinopril and n=34 in placebo group.

Treatment effect was also analysed according to baseline AER using four categories: <5, 5-<10, 10-<20 and 20-200 µg/min and statistical difference was reached in none of these categories.

Furthermore, a separate analysis (not predefined) was performed after adjustment for baseline AER and centre, and only patients who attended the final visit were included in this analysis. This analysis showed that the treatment group difference was 0.23 µg/min in patients with normoalbuminuria (p=0.6) and 38.5 µg/min in patients with microalbuminuria (p<0.001).

Changes in albuminuric status did not show significant differences between the treatment groups

Changes in AER and other factors: The relative % difference in AER at 24 months was only significant in the subgroups of patients with poor glycaemic control (HbA_{1c}>7%), in women, and in patients with baseline DBP<80 mmHg.

Secondary endpoints

GFR: Approximately 10% of GFR measurements were excluded from analysis, as the values were below 30 ml/min/1.73m^2 which were judged inconsistent with other assessments of renal function and attributable to problems in collection of blood samples. After 24 months, GFR increased from baseline similarly in lisinopril (4.7 ml/min/1.73m^2) and in placebo (4.6 ml/min/1.73m^2) groups.

Sitting BP: The treatment differences in mean reduction in both SBP and DBP were significant (8.2 and 6.7 in the lisinopril vs 4.5 ($p<0.0004$) and 4.7 ($p<0.006$) mmHg in the placebo groups, respectively). This difference might have been caused by the fact that the BP reduction aimed at DBP <75mmHg by doubling the lisinopril or placebo dose, while nifedipine was allowed only if SBP >160 or DBP >95 mmHg in both groups.

Retinopathy
Retinal photographs of two 45° fields of each eye were taken at baseline and 24 months by trained photographers. Slides of the photographs were graded by an expert at the retinal grading centre, without knowledge of treatment assignment.

Patients were assigned to 1 of 6 retinopathy levels by the worst affected eye:
- level 0 - no retinopathy
- level 1 - minimal non-proliferative retinopathy
- level 2 - moderate non-proliferative retinopathy
- level 3 - severe non-proliferative retinopathy
- level 4 - photocoagulated retinopathy
- level 5 - proliferative retinopathy

The main outcome parameter was the progression of retinopathy by at least 1 level. Those who could not progress (levels 4 and 5) were excluded from the analyses.

Progression by at least 2 levels was also examined, and those with levels 3,4 or 5 at baseline were excluded in this case.

The incidence of new retinopathy was examined in those who had no retinopathy at baseline. Progression to proliferative retinopathy or photocoagulation (levels 4 or 5) was examined in those with no or non-proliferative retinopathy at baseline.

Odds ratios were calculated and adjustment for centre was included in the protocol. Adjustments were made using logistic regression.

The prevalence of retinopathy at baseline was 59% (103/175) in the lisinopril group and 65% (117/179) in the placebo group (p=0.2).

There were significant treatment differences in favour of lisinopril regarding progression and regression (Table 3). However, after adjustment for centre and/or glycaemic control, the only statistical significance that remained was the difference in progression to levels 4 or 5.

Table 3 Progression or regression of retinopathy at 24 months

	Lisinopril (%)	Placebo (%)	Odds ratio (95% CI)	p value

Progression by at least 1 level	21/159 (13)	39/166 (23)	0.50 (0.28, 0.89)	0.02[1]
Progression by at least 2 level	3/157 (2)	11/166 (7)	0.27 (0.07, 1.00)	0.05[2]
Progression to levels 4 or 5	2/159 (1)	11/166 (7)	0.18 (0.04, 0.82)	0.03
Incidence of new retinopathy	13/72 (18)	15/62 (24)	0.69 (0.30, 1.59)	0.4
Regression by at least 1 level	33/103 (32)	28/117 (24)	1.48 (0.82, 2.68)	0.2

After adjustment for centre and centre plus glycaemic control, the odds ratio became 0.5 (0.28, 0.92; p=0.03)) and 0.55 (p=0.06), respectively.

1. Adjustment for HbA_{1C} at baseline attenuated the odds ratio to 0.30 (p=0.07).

Systolic BP was 3 mmHg lower in the lisinopril group than in the placebo group during the study. After adjustment for this difference in SBP, the odds ratio for progression to levels 4 or 5 was attenuated to 0.57 and became insignificant (p=0.09).

In summary, trial 306 (EUCLID) was ill suited to provide the documentation to support the proposed claim in incipient nephropathy. Only a minority of the enrolled patients belonged to the suggested target population of normotensive IDDM patients with microalbuminuria, and in this group statistically significant efficacy of lisinopril over placebo could not be demonstrated in predefined analyses.

Significant beneficial effects of lisinopril on retinopathy in IDDM patients, in addition to the effects of blood pressure lowering and glycaemic control, were not demonstrated.

Incipient nephropathy in hypertensive NIDDM patients (study 298)

Study 298 (BRILLIANT) was a randomised, parallel-group trial of lisinopril (n=168) versus nifedipine (n=167) on AER and BP control in 59 European centres. For inclusion, patients should be male 18-75 years or post-menopausal/non-fertile female patients aged 40-75 years with type 2 diabetes at least 3 months from diagnosis, clinically stable on oral hypoglycaemics and/or dietary advice, and with incipient nephropathy (AER 20-300 ug/min) at some time within a 6 month screening period prior to entry to the run-in and confirmed before randomisation, sitting DBP 90-110 mmHg during run-in, and anti-hypertensive treatment withdrawn at least 2-4 weeks before the start of run-in.

Lisinopril 10 mg od or nifedipine SR 20 mg bd was given orally. The dose should be doubled if DBP was greater than 90 mmHg at any visit after randomisation, and changed back if at any subsequent time the investigator thought it appropriate. Additional medication, frusemide, could be given if DBP was higher than 90 mmHg despite the higher treatment doses. Patients with a sitting DBP ≥120 mmHg at any time during the study were withdrawn.

The primary efficacy endpoints were the change from baseline to 12 months in urinary albumin excretion (AER) and BP. Secondary endpoints were HbA_{1C}, creatinine clearance, lipids and haemostatic factors.

Primary efficacy outcomes

Lisinopril-treated patients were shown to have a 20 ug/min larger reduction in the median of AER, compared with nifedipine SR-treated patients at both 6 and 12 months (Table 4). However, no difference was found in creatinine clearance between treatment groups (Table 5).

Table 4 AER (ug/min) in the treatment groups

	Lisinopril	Nifedipine SR	Treatment difference (lisinopril-nifedipine)*
Baseline	n=156; Mean=91.4 Median=65.5; Range=20-297	n=158; Mean=86.6; Median=63.0; Range=20-289	
12 months	n=123; Mean=73.6; Median=39.0; Range=2-510	n=123; Mean=100.0; Median=58.0; Range=9-1192	
Change from baseline to 6 months	n=134; Median= -24.5	n=130; Median= -8.0	-20 (median); 95% CI: -30; -10 p=0.0002
Change from baseline to 12 months	n=123; Median= -17.0	n=123; Median= -2.0	-20 (median); 95% CI: -32; -9 p=0.0006

* The treatment difference was not lisinopril median - nifedipine median.

Table 5 Creatinine clearance (mean and SD)

	Lisinopril	Nifedipine
Baseline	102; 46	99; 40
At 6 months	105; 50	108; 46
At 12 months	105; 54	105; 60

Analysis of sitting BP showed numerical, although statistically not significant differences in the reduction of SBP and DBP between treatment groups after 12 months (13 and 9.5 mmHg in the lisinopril group, and 11 (p=0.27) and 10 mmHg (p=0.49) in the nifedipine SR group, respectively.

The highest allowed dose was used in 48% of lisinopril-treated patients (20 mg od) and in 46% of nifedipine SR-treated patients (40 mg bd) (p=0.6). However, a greater proportion of patients treated with lisinopril received additional frusemide (27%) compared with patients treated with nifedipine SR (17%; p=0.055).

HbA_{1c} increased slightly in both treatment groups from baseline to 12 months (7.5 to 7.8 in lisinopril group and 7.6 to 7.8 in nifedipine SR group, p=0.27).

Other data used to support the indication can be summarised as follows:

Normotensive IDDM
A number of trials with different ACEi have been performed in this population and show reduced AER and reduced progression to macroalbuminuria. As far as is understood, there are no further ACEi trials focusing on retinopathy.

Hypertensive NIDDM
The expert report makes reference to micro-HOPE (ramipril) and RENAAL (losartan), which provided clinical outcome data. The IDNT and IRMA-2 (irbesartan) could also be taken into account

It is accepted that ACEi is established first-line therapy in patients with IDDM and any degree of hypertension. The definition of "normotension" may be elusive in this population. Generically, ACEi reduce microalbuminuria in IDDM, to an extent that may not be fully accounted for by blood pressure reduction. The documentation from EUCLID is considered too weak to warrant an indication specific to Zestril, however: Overall, reduction of AER *vs.* placebo in this trial was marginally significant when adjusted for BP, and efficacy could not be demonstrated in the target population with microalbuminuria at baseline, which was insufficiently represented in the trial. The effects on retinopathy in the study population were not convincing after adjustment for BP and glycaemic control and are not further supported by external data.

In hypertensive NIDDM with (incipient) nephropathy, there is strong external support for the benefit of RAAS modulation. The BRILLIANT study was deficient in its short duration and in that it was not able to show effects on GFR.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Zestril, the following was considered to be the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications

Hypertension
Treatment of hypertension.

Heart Failure
Treatment of symptomatic heart failure.

Acute Myocardial Infarction
Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.

Renal Complications of Diabetes Mellitus
Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy (see section 5.1).

Section 4.2. Posology and method of administration

The MAH was requested to substantiate scientifically the divergent information across member states and justify a proposed common wording, especially with regard to therapeutic daily dose range.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Zestril the following was considered to be the most suitable harmonised Section 4.2 Posology text:

4.2 Posology and method of administration

Zestril should be administered orally in a single daily dose. As with all other medication taken once daily, Zestril should be taken at approximately the same time each day. The absorption of Zestril tablets is not affected by food.

The dose should be individualised according to patient profile and blood pressure response (see section 4.4)

Hypertension
Zestril may be used as monotherapy or in combination with other classes of antihypertensive medicinal products.

Starting dose
In patients with hypertension the usual recommended starting dose is 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and /or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment (see Table 1 below).

Maintenance dose

The usual effective maintenance dosage is 20 mg administered in a single daily dose. 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 80 mg/day.

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 2 to 3 days before beginning therapy with Zestril. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Zestril should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Zestril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5).

Dosage Adjustment In Renal Impairment

Dosage in patients with renal impairment should be based on creatinine clearance as outlined in Table 1 below.

Table 1 Dosage adjustment in renal impairment.

Creatinine Clearance (ml/min)	Starting Dose (mg/day)
Less than 10 ml/min (including patients on dialysis)	2.5 mg*
10-30 ml/min	2.5-5 mg
31-80 ml/min	5-10 mg

* 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 40 mg daily.

Heart Failure

In patients with symptomatic heart failure, Zestril should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. Zestril may be initiated at a starting dose of 2.5 mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of Zestril should be increased:

- By increments of no greater than 10 mg
- At intervals of no less than 2 weeks
- To the highest dose tolerated by the patient up to a maximum of 35 mg 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. Renal function and serum potassium should be monitored (see section 4.4).

Acute Myocardial Infarction

Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with Zestril.

Starting dose (first 3 days after infarction)

Treatment with Zestril may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Zestril is 5 mg given

orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4).

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Zestril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Maintenance dose
The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) Zestril should be withdrawn.

Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Zestril (see section 4.2).

Renal Complications of Diabetes Mellitus
In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg Zestril once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg.

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Zestril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Paediatric Use
Efficacy and safety of use in children has not been fully established. Therefore, use in children is not recommended.

Use In The Elderly
In clinical studies, there was no age-related change in the efficacy or safety profile of the drug. When advanced age is associated with decrease in renal function, however, 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.

Use in kidney transplant patients
There is no experience regarding the administration of Zestril in patients with recent kidney transplantation. Treatment with Zestril is therefore not recommended.

Safety issues

Section 4.3 Contraindications
The MAH was requested to propose and scientifically justify a common EU wide approach as the contraindications text was considered to differ to a large extent between Member States especially relating to:

- Bilateral renal artery stenosis or unilateral renal artery stenosis in patients with only one kidney.
- After kidney transplantation.
- Systolic blood pressure $\leq$ 100 mmHg before initiation of the treatment with lisinopril.
- Haemodynamically relevant aortic or mitral valve stenosis or hypertrophic cardiomyopathy.
- Pregnancy and lactation.
- Concurrent use of lisinopril and poly (acrylonitrile, sodium-2-methylallyl-sulphonate) high-flux membranes (e.g. AN 69) for emergency dialysis.
- Cardiogenic shock.
- Severe renal impairment.
- Dialysis.

- Haemodynamically unstable patients after acute myocardial infarction.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Zestril, the following was considered to be the most suitable harmonised Section 4.3 Contraindications, the text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices:

4.3 Contraindications

- Hypersensitivity to Zestril, to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor.
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second or third trimesters of pregnancy (see section 4.6)

Section 4.4. Special warnings and precautions for use

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Zestril, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (See Annex III). The text in the harmonised SPC is not so dissimilar to the currently approved SPCs that it will significantly change clinical practices.

All other sections of the SPC were harmonised as a result of the referral procedure (except See Below; Administrative Issues).

Administrative issues

Other sections of the SPC which were not harmonised and which need to be introduced nationally by the Member States when implementing the harmonised SPC are the following: MAH, MA number, date of first authorisation/renewal of authorisation, Date of revision of the text.

Benefit/Risk considerations

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Zestril is favourable for use relating to treatment-resistant schizophrenic patients and psychotic disorders occurring during the course of Parkinson's disease in cases where standard treatment has failed.

GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS

Whereas,

- The scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- The Summary of Products Characteristic proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

The CPMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III of the Opinion. The divergences identified at the start of the referral have been resolved.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was Annexed to the Commission Decision on this Article 30 referral for lisinopril containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

Zestril, 2.5 mg, tablets.
Zestril, 5 mg, tablets.
Zestril, 10 mg, tablets.
Zestril, 20 mg, tablets.
Zestril, 30 mg, tablets.
Zestril, 40 mg, tablets.

[To be implemented nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains lisinopril dihydrate equivalent to 2.5 mg anhydrous lisinopril.
Each tablet contains lisinopril dihydrate equivalent to 5 mg anhydrous lisinopril.
Each tablet contains lisinopril dihydrate equivalent to 10 mg anhydrous lisinopril.
Each tablet contains lisinopril dihydrate equivalent to 20 mg anhydrous lisinopril.
Each tablet contains lisinopril dihydrate equivalent to 30 mg anhydrous lisinopril.
Each tablet contains lisinopril dihydrate equivalent to 40 mg anhydrous lisinopril.

For excipients, see 6.1 List of excipients.
[To be implemented nationally]

3. PHARMACEUTICAL FORM

Tablets.
2.5 mg tablets are white, round and biconvex. They have a diameter of 6 mm.
5 mg tablets are pink, round and biconvex. They have a diameter of 6 mm.
10 mg tablets are pink, round and biconvex. They have a diameter of 8 mm.
20 mg tablets are pink, round and biconvex. They have a diameter of 8 mm.
30 mg tablets are pink, round and biconvex. They have a diameter of 9 mm.
40 mg tablets are yellow, round and biconvex. They have a diameter of 9 mm.

All tablets are marked on one side with a number denoting the tablet strength.
[To be implemented nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of hypertension.

Heart Failure
Treatment of symptomatic heart failure.

Acute Myocardial Infarction
Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.

Renal Complications of Diabetes Mellitus

Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy (see section 5.1).

4.2 Posology and method of administration

Zestril should be administered orally in a single daily dose. As with all other medication taken once daily, Zestril should be taken at approximately the same time each day. The absorption of Zestril tablets is not affected by food.

The dose should be individualised according to patient profile and blood pressure response (see section 4.4)

Hypertension
Zestril may be used as monotherapy or in combination with other classes of antihypertensive medicinal products.

Starting dose
In patients with hypertension the usual recommended starting dose is 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (in particular, renovascular hypertension, salt and /or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 2.5-5 mg is recommended in such patients and the initiation of treatment should take place under medical supervision. A lower starting dose is required in the presence of renal impairment (see Table 1 below).

Maintenance dose
The usual effective maintenance dosage is 20 mg administered in a single daily dose. 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 80 mg/day.

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 2 to 3 days before beginning therapy with Zestril. In hypertensive patients in whom the diuretic cannot be discontinued, therapy with Zestril should be initiated with a 5 mg dose. Renal function and serum potassium should be monitored. The subsequent dosage of Zestril should be adjusted according to blood pressure response. If required, diuretic therapy may be resumed (see section 4.4 and section 4.5).

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

Table 1 Dosage adjustment in renal impairment.

Creatinine Clearance (ml/min)	Starting Dose (mg/day)
Less than 10 ml/min (including patients on dialysis)	2.5 mg*
10-30 ml/min	2.5-5 mg
31-80 ml/min	5-10 mg

* 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 40 mg daily.

Heart Failure
In patients with symptomatic heart failure, Zestril should be used as adjunctive therapy to diuretics and, where appropriate, digitalis or beta-blockers. Zestril may be initiated at a starting dose of 2.5 mg once a day, which should be administered under medical supervision to determine the initial effect on the blood pressure. The dose of Zestril should be increased:

- By increments of no greater than 10 mg
- At intervals of no less than 2 weeks
- To the highest dose tolerated by the patient up to a maximum of 35 mg 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. Renal function and serum potassium should be monitored (see section 4.4).

Acute Myocardial Infarction
Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin, and beta-blockers. Intravenous or transdermal glyceryl trinitrate may be used together with Zestril.

Starting dose (first 3 days after infarction)
Treatment with Zestril may be started within 24 hours of the onset of symptoms. Treatment should not be started if systolic blood pressure is lower than 100 mm Hg. The first dose of Zestril is 5 mg given orally, followed by 5 mg after 24 hours, 10 mg after 48 hours and then 10 mg once daily. Patients with a low systolic blood pressure (120 mm Hg or less) when treatment is started or during the first 3 days after the infarction should be given a lower dose - 2.5 mg orally (see section 4.4).

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Zestril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Maintenance dose
The maintenance dose is 10 mg once daily. If hypotension occurs (systolic blood pressure less than or equal to 100 mm Hg) a daily maintenance dose of 5 mg may be given with temporary reductions to 2.5 mg if needed. If prolonged hypotension occurs (systolic blood pressure less than 90 mm Hg for more than 1 hour) Zestril should be withdrawn.

Treatment should continue for 6 weeks and then the patient should be re-evaluated. Patients who develop symptoms of heart failure should continue with Zestril (see section 4.2).

Renal Complications of Diabetes Mellitus
In hypertensive patients with type 2 diabetes mellitus and incipient nephropathy, the dose is 10 mg Zestril once daily which can be increased to 20 mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90 mm Hg.

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Zestril dosage should be adjusted according to the patient's creatinine clearance (see Table 1).

Paediatric Use
Efficacy and safety of use in children has not been fully established. Therefore, use in children is not recommended.

Use In The Elderly

In clinical studies, there was no age-related change in the efficacy or safety profile of the drug. When advanced age is associated with decrease in renal function, however, 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.

Use in kidney transplant patients
There is no experience regarding the administration of Zestril in patients with recent kidney transplantation. Treatment with Zestril is therefore not recommended.

4.3 Contraindications

- Hypersensitivity to Zestril, to any of the excipients or any other angiotensin converting enzyme (ACE) inhibitor
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second or third trimesters of pregnancy (see section 4.6)

4.4 Special warnings and special precautions for use

Symptomatic Hypotension
Symptomatic hypotension is 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, or has severe renin-dependent hypertension (see section 4.5 and section 4.8). In patients with 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, hyponatraemia or functional renal impairment. In patients at increased risk of symptomatic hypotension, initiation of therapy and dose adjustment should be closely monitored. 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 contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with 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. If hypotension becomes symptomatic, a reduction of dose or discontinuation of Zestril may be necessary.

Hypotension In Acute Myocardial Infarction
Treatment with Zestril 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 100 mm Hg or lower or those in cardiogenic shock. During the first 3 days following the infarction, the dose should be reduced if the systolic blood pressure is 120 mm Hg or lower. Maintenance doses should be reduced to 5 mg or temporarily to 2.5 mg if systolic blood pressure is 100 mm Hg or lower. If hypotension persists (systolic blood pressure less than 90 mm Hg for more than 1 hour) then Zestril should be withdrawn.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy
As with other ACE inhibitors, Zestril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal Function Impairment

In cases of renal impairment (creatinine clearance <80 ml/min), the initial Zestril dosage should be adjusted according to the patient's creatinine clearance (see Table 1 in section 4.2) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine is part of normal medical practice for these patients.

In patients with heart failure, hypotension following the initiation of therapy with ACE inhibitors may lead to some further impairment in renal function. Acute renal failure, usually reversible, has been reported in this situation.

In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, who have been treated with angiotensin converting enzyme inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also 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. This is 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 Zestril should not be initiated in patients with evidence of renal dysfunction, defined as serum creatinine concentration exceeding 177 micromol/l and/or proteinuria exceeding 500 mg/24 h. 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.

Hypersensitivity/Angioedema
Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported rarely in patients treated with angiotensin converting enzyme inhibitors, including Zestril. This may occur at any time during therapy. In such cases, Zestril should be discontinued promptly and appropriate treatment and monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patients. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient.

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 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 of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see 4.3 Contraindications).

Anaphylactoid reactions in Haemodialysis Patients
Anaphylactoid reactions have been reported in patients dialysed with high flux membranes (e.g. 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.

Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis
Rarely, patients receiving ACE inhibitors during low-density lipoproteins (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Desensitisation
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.

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 Zestril who develop jaundice or marked elevations of hepatic enzymes should discontinue Zestril and receive appropriate medical follow-up.

Neutropenia/ Agranulocytosis
Neutropenia/ Agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Neutropenia and agranulocytosis are reversible after discontinuation of the ACE inhibitor. Zestril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If Zestril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection.

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

As with other ACE inhibitors, Zestril may be less effective in lowering blood pressure in black patients than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

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.

Hyperkalaemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including Zestril. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes, or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

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)

Lithium
The combination of lithium and Zestril is generally not recommended (see section 4.5).

Pregnancy and lactation
Lisinopril should not be used during the first trimester of pregnancy. Zestril is contraindicated in the second and third trimesters of pregnancy (see section 4.3). When pregnancy is detected, lisinopril treatment should be discontinued as soon as possible (see section 4.6).

Use of lisinopril is not recommended during breast-feeding.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics
When a diuretic is added to the therapy of a patient receiving Zestril the antihypertensive effect is usually additive.

Patients already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure when Zestril is added. The possibility of symptomatic hypotension with Zestril can be minimised by discontinuing the diuretic prior to initiation of treatment with Zestril (see section 4.4).

Potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes
Although in clinical trials, serum potassium usually remained within normal limits, hyperkalaemia did occur in some patients. Risk factors for the development of hyperkalaemia include renal insufficiency, diabetes mellitus, and concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene or amiloride), potassium supplements or potassium-containing salt substitutes. The use of potassium supplements, potassium-sparing diuretics or potassium-containing salt substitutes, particularly in patients with impaired renal function, may lead to a significant increase in serum potassium.

If Zestril is given with a potassium-losing diuretic, diuretic-induced hypokalaemia may be ameliorated.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACE inhibitors. Use of Zestril with lithium is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels should be performed (see section 4.4).

Non steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid = 3G/day
Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor. NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Other antihypertensive agents
Concomitant use of these agents may increase the hypotensive effects of Zestril. Concomitant use with glyceryl trinitrate and other nitrates, or other vasodilators, may further reduce blood pressure.

Tricyclic antidepressants / Antipsychotics /Anaesthetics

Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see section 4.4)

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

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.

Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates
Zestril may be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers and/or nitrates.

4.6 Pregnancy and lactation

Pregnancy
Zestril should not be used during the first trimester of pregnancy. When pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester toxicity exposure have not appeared to manifest malformations consistent with human foetotoxicity as described below.
Zestril is contraindicated during the second and third trimester of pregnancy (see section 4.3).

Prolonged ACE inhibitor exposure during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia, see also section 5.3).

Should exposure to Zestril have occurred from the second trimester of pregnancy, an ultrasound check of renal function and the skull is recommended.

Infants whose mothers have taken Zestril should be closely observed for hypotension, oliguria and hyperkalaemia. Zestril, which crosses the placenta, has been removed from the neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion.

Lactation
It is not known whether Zestril is excreted into human breast milk. Lisinopril is excreted into the milk of lactating rats. The use of Zestril is not recommended in women who are breast-feeding.

4.7 Effects on ability to drive and use machines
When driving vehicles or operating machines it should be taken into account that occasionally dizziness or tiredness may occur.

4.8 Undesirable effects
The following undesirable effects have been observed and reported during treatment with Zestril and other ACE inhibitors with the following frequencies: Very common (≥10%), common (≥1%,<10%), uncommon (≥0.1,<1%), rare (≥0.01,<0.1%), very rare (<0.01%) including isolated reports.

Blood and the lymphatic system disorders:
rare: decreases in haemoglobin, decreases in haematocrit.

very rare: bone marrow depression, anaemia, thrombocytopenia, leucopenia, neutropenia, agranulocytosis (see section 4.4), haemolytic anaemia, lymphadenopathy, autoimmune disease

Metabolism and nutrition disorders
very rare: hypoglycaemia

Nervous system and psychiatric disorders:
common: dizziness, headache
uncommon: mood alterations, paraesthesia, vertigo, taste disturbance, sleep disturbances.
rare: mental confusion

Cardiac and vascular disorders:
common: orthostatic effects (including hypotension)
uncommon: myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see section 4.4), palpitations, tachycardia. Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:
common: cough
uncommon: rhinitis
very rare: bronchospasm, sinusitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:
common: diarrhoea, vomiting
uncommon: nausea, abdominal pain and indigestion
rare: dry mouth
very rare: pancreatitis, intestinal angioedema, hepatitis- either hepatocellular or cholestatic, jaundice and hepatic failure (see section 4.4)

Skin and subcutaneous tissue disorders:
uncommon: rash, pruritus
rare: hypersensitivity/angioneurotic oedema: angioneurotic oedema of the face, extremities, lips, tongue, glottis, and/or larynx (see section 4.4), urticaria, alopecia, psoriasis
very rare: diaphoresis, pemphigus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme.

A symptom complex has been reported which may include one or more of the following: fever, vasculitis, myalgia, arthralgia/arthritis, a positive antinuclear antibodies (ANA), elevated red blood cell sedimentation rate (ESR), eosinophilia and leucocytosis, rash, photosensitivity or other dermatological manifestations may occur.

Renal and urinary disorders:
common: renal dysfunction
rare: uraemia, acute renal failure
very rare: oliguria/anuria

Reproductive system and breast disorders:
uncommon: impotence
rare gynaecomastia

General disorders and administration site conditions:
uncommon: fatigue, asthenia

Investigations:
uncommon: increases in blood urea, increases in serum creatinine, increases in liver enzymes, hyperkalaemia
rare: increases in serum bilirubin, hyponatraemia.

4.9 Overdose
Limited data are available for overdose in humans. Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety and cough.

The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating Zestril (e.g., emesis, gastric lavage, administration of absorbents and sodium sulphate). Zestril may be removed from the general circulation by haemodialysis (see section 4.4). Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored frequently.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC code: C09A A03

Zestril 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.

Whilst 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.

The effect of Zestril on mortality and morbidity in 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.

In the GISSI-3 trial, which used a 2x2 factorial design to compare the effects of Zestril and glyceryl trinitrate given alone or in combination for 6 weeks versus control in 19,394, patients who were administered the treatment within 24 hours of an acute myocardial infarction, Zestril produced a statistically significant risk reduction in mortality of 11% versus control ($2p=0.03$). The risk reduction

with glyceryl trinitrate was not significant but the combination of Zestril and glyceryl trinitrate produced a significant risk reduction in mortality of 17% versus control (2p=0.02). In the sub-groups of elderly (age > 70 years) and females, pre-defined as patients at high risk of mortality, significant benefit was observed for a combined endpoint of mortality and cardiac function. The combined endpoint for all patients, as well as the high-risk sub-groups, at 6 months also showed significant benefit for those treated with Zestril or Zestril plus glyceryl trinitrate for 6 weeks, indicating a prevention effect for Zestril. As would be expected from any vasodilator treatment, increased incidences of hypotension and renal dysfunction were associated with Zestril treatment but these were not associated with a proportional increase in mortality.

In a double-blind, randomised, multicentre trial which compared Zestril with a calcium channel blocker in 335 hypertensive Type 2 diabetes mellitus subjects with incipient nephropathy characterised by microalbuminuria, Zestril 10 mg to 20 mg administered once daily for 12 months, reduced systolic/diastolic blood pressure by 13/10 mmHg and urinary albumin excretion rate by 40%. When compared with the calcium channel blocker, which produced a similar reduction in blood pressure, those treated with Zestril showed a significantly greater reduction in urinary albumin excretion rate, providing evidence that the ACE inhibitory action of Zestril reduced microalbuminuria by a direct mechanism on renal tissues in addition to its blood pressure lowering effect.

Lisinopril treatment does not affect glycaemic control as shown by a lack of significant effect on levels of glycated haemoglobin (HbA_{1c}).

5.2 Pharmacokinetic properties

Lisinopril is an orally active non-sulphydryl-containing ACE inhibitor.

Absorption

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. Based on urinary recovery, the mean extent of absorption of lisinopril is approximately 25% with inter-patient variability of 6-60% over the dose range studied (5-80 mg). The absolute bioavailability is reduced approximately 16% in patients with heart failure. Lisinopril absorption is not affected by the presence of food.

Distribution

Lisinopril does not appear to be bound to serum proteins other than to circulating angiotensin converting enzyme (ACE). Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly.

Elimination

Lisinopril does not undergo metabolism and is excreted entirely unchanged into the urine. On multiple dosing lisinopril has an effective half-life of accumulation of 12.6 hours. The clearance of lisinopril in healthy subjects is approximately 50 ml/min. 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.

Hepatic impairment

Impairment of hepatic function in cirrhotic patients resulted in a decrease in lisinopril absorption (about 30% as determined by urinary recovery) but an increase in exposure (approximately 50%) compared to healthy subjects due to decreased clearance.

Renal impairment

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. In mild to moderate renal impairment (creatinine clearance 30-80 ml/min) mean AUC was increased by 13% only, while a 4.5-fold increase in mean AUC was observed in severe renal impairment (creatinine clearance 5-30 ml/min).

Lisinopril can be removed by dialysis. During 4 hours of haemodialysis, plasma lisinopril concentrations decreased on average by 60%, with a dialysis clearance between 40 and 55 ml/min.

Heart failure
Patients with heart failure have a greater exposure of lisinopril when compared to healthy subjects (an increase in AUC on average of 125%), but based on the urinary recovery of lisinopril, there is reduced absorption of approximately 16% compared to healthy subjects.

Elderly
Older patients have higher blood levels and higher values for the area under the plasma concentration time curve (increased approximately 60%) compared with younger subjects.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on the late foetal development, resulting in foetal death and congenital effects, in particular affecting the skull. Foetotoxicity, intrauterine growth retardation and patent ductus arteriosus have also been reported. These developmental anomalies are thought to be partly due to a direct action of ACE inhibitors on the foetal renin-angiotensin system and partly due to ischaemia resulting from maternal hypotension and decreases in foetal-placental blood flow and oxygen/nutrients delivery to the foetus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be implemented nationally]

6.2 Incompatibilities

[To be implemented nationally]

6.3 Shelf life

[To be implemented nationally]

6.4 Special precautions for storage

[To be implemented nationally]

6.5 Nature and contents of container

[To be implemented nationally]

6.6 Instructions for use and handling

[To be implemented nationally]

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

