The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

September 2003
CPMP/869/04/Final

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
OPINION FOLLOWING AN ARTICLE 7(5) REFERRAL

Cardiostad (lisinopril)

International non-proprietary name (INN): Lisinopril

BACKGROUND INFORMATION

Cardiostad (lisinopril), which contains the active ingredient lisinopril is a highly specific, competitive inhibitor of angiotensin-I converting enzyme and therefore belongs to the group of drugs known as ACE inhibitors. Lisinopril is indicated for the treatment of hypertension, heart failure, acute myocardial infarction and, in some EU Member States, incipient nephropathy.

The Marketing Authorisation Holder (MAH) for Cardiostad (lisinopril) applied to the Reference Member State (Denmark) for a variation through the Mutual Recognition Procedure to add an indication: "treatment of incipient nephropathy in diabetes characterised by microalbuminura." This was refused by the RMS because they would not accept an indication that was not approved for the reference product Zestril (and associated names) unless the MAH could submit sufficient clinical data of its own.

In the Netherlands, Zestril does have the diabetic nephropathy indication and since Cardiostad (lisinopril) is claimed to be essentially similar to Zestril and will be used as a substitute, the Dutch Medicines Evaluation Board was of the opinion that refusal of the variation could cause a safety issue and a risk to public health because of differences in indications in the Summary of Product Characteristics and in the patient information leaflets. On 17th July 2002, the Netherlands referred the matter to the CPMP with further clarification on 23 July 2002.

The referral procedure started on 26th July 2002. The Rapporteur and Co-Rapporteur appointed were Dr. P. Nilsson and Prof R. Bass, respectively. Written explanations were provided by the Marketing Authorisation Holders on 20th November 2002, 27 May 2003 and 25 June 2003.

Based on evaluation of the currently available data and the Rapporteurs' assessment reports, the CPMP considered that the data did not support the indication in normotensive insulin dependent diabetes mellitus patients but that a revised indication: "Treatment of renal disease in hypertensive patients with type 2 diabetes melitus and incipient nephropathy" could be granted. The CPMP therefore adopted an opinion on 24 July 2003 recommending the above variation to the Marketing Authorisations together with an amended Summary of Product Characteristics.

The competent authorites of the Member States will continue to keep the product under regular review.

A list of product names concerned is given in Annex I. The scientific conclusions are provided in Annex II, together with the amended Summary of Product Characteristics in Annex III.

The final opinion was converted into a Decision by the European Commission on 23 February 2004.

* **Notes**: The information given in this document and Annexes reflect only the CPMP Opinion dated 24 July 2003. The Member States competent authorities will continue to keep the product under regular review.

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ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, 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	STADA Arzneimittel Ges.m.b.H, Heiligenstädter Straße 52/2/8, 1190 Wien, Austria	Lisinostad	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Austria	STADA Arzneimittel Ges.m.b.H, Heiligenstädter Straße 52/2/8, 1190 Wien, Austria	Lisinostad	10 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Austria	STADA Arzneimittel Ges.m.b.H, Heiligenstädter Straße 52/2/8, 1190 Wien, Austria	Lisinostad	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Belgium	Eurogenerics, Heizel Esplanade b22, 1020 Brussel, Belgium	Lisinopril EG	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Belgium	Eurogenerics Heizel Esplanade b22 1020 Brussel Belgium	Lisinopril EG	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Denmark	STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, Germany	Cardiostad	5 mg	Tablet	Oral use	Blister (PVC/Alu)	20, 28, 30, 50, 98, 100, tablets
Denmark	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Cardiostad	10 mg	Tablet	Oral use	Blister (PVC/Alu)	20, 28, 30, 50, 98, 100, tablets

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Denmark	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Cardiostad	20 mg	Tablet	Oral use	Blister (PVC/Alu)	20, 28, 30, 50, 98, 100, tablets
Finland	STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, Germany	Cardiostad	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Finland	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Cardiostad	10 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Finland	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Cardiostad	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Germany	STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, Germany	Cardiostad	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Germany	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Cardiostad	10 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Germany	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Cardiostad	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Ireland	Clonmel Healthcare, Waterford Road, Clonmel, Co. Tipperary, Ireland	Zestan	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Ireland	Clonmel Healthcare, Waterford Road, Clonmel, Co. Tipperary, Ireland	Zestan	10 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Ireland	Clonmel Healthcare, Waterford Road, Clonmel, Co. Tipperary, Ireland	Zestan	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Italy	Laboratori Euro Generici, Via Domenico Scarlatti 31, 20124 Milano, Italy	Lisinopril EG	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Italy	Laboratori Euro Generici Via Domenico Scarlatti 31 20124 Milano Italy	Lisinopril EG	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
The Netherlands	Centrafarm Services B.V., Nieuwe Donk 9, 4879 Etten-Leur, The Netherlands	Lisinopril CF	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
The Netherlands	Centrafarm Services B.V. Nieuwe Donk 9 4879 Etten-Leur The Netherlands	Lisinopril CF	10 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
The Netherlands	Centrafarm Services B.V. Nieuwe Donk 9 4879 Etten-Leur The Netherlands	Lisinopril CF	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Portugal	Stada Arzneimittel A.G. Stadastrasse 2-18 D-61118 Bad Vilbel Alemanha	Lisinopril Ciclum	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Portugal	Stada Arzneimittel A.G. Stadastrasse 2-18 D-61118 Bad Vilbel Alemanha	Lisinopril Ciclum	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Spain	STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, Germany	Lisinocic	5 mg	Tablet	Oral use	Blister (PVC/Alu)	60, 500 tablets
Spain	STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, Germany	Lisinocic	20 mg	Tablet	Oral use	Blister (PVC/Alu)	60, 500 tablets
Sweden	STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, Germany	Lisinopril Stada	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Sweden	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Lisinopril Stada	10 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
Sweden	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Lisinopril Stada	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
United Kingdom	STADA Arzneimittel AG, Stadastrasse 2-18, 61118 Bad Vilbel, Germany	Lisinopril	5 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets
United Kingdom	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel	Lisinopril	10 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500,

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
	Germany						1000 tablets
United Kingdom	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel Germany	Lisinopril	20 mg	Tablet	Oral use	Blister (PVC/Alu)	14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 250, 300, 400, 500, 1000 tablets

ANNEX II

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

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF CARDIOSTAD (lisinopril) AND ASSOCIATED NAMES (SEE ANNEX I)

Lisinopril is a highly specific, competitive inhibitor of angiotensin-I converting enzyme and therefore belongs to the group of drugs known as ACE inhibitors. Lisinopril is indicated for the treatment of hypertension, heart failure, acute myocardial infarction and, in some EU Member States, incipient diabetic nephropathy.

The MAH for Cardiostad (lisinopril) applied to the Reference Member State (RMS) for a variation through the Mutual Recognition Procedure to add an indication: "treatment of incipient nephropathy in diabetes characterised by microalbuminuria." The reference product, Zestril (and associated names), does not have the same indications in all Member States due to divergent national decisions. In particular it is not authorised for the "treatment of incipient nephropathy in diabetes characterised by microalbuminuria" in Denmark which is the RMS for Cardiostad (lisinopril). The RMS would not accept an indication, which is not approved for the reference product, unless the MAH could submit sufficient clinical data of its own. Therefore the variation could not be granted.

In the Netherlands, Zestril does have the indication "incipient nephropathy in diabetes characterised by microalbuminuria." Since Cardiostad (lisinopril) is claimed to be essentially similar to Zestril and will be used as a substitute, the Dutch Medicines Evaluation Board (MEB) is of the opinion that refusal of the variation could cause a safety issue and a risk to public health and therefore referred the issue to the CPMP.

The CPMP considered the documentation provided by the MAH and came to the following conclusions:

Efficacy

The two pivotal trials which formed the supporting documentation for the proposed indication were Study 306 "EUCLID" (Lancet 1997; 349: 1787-1792) and Study 298 "BRILLIANT" (J Hum Hypertens 1996; 10: 185-192)

Study 306 EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes (EUCLID)

This was a European multicentre randomised, double blind, parallel group, placebo controlled trial of lisinopril in "normotensive" insulin dependent diabetes mellitus (IDDM) patients. Five hundred and thirty patients were randomised to receive lisinopril (n=265) or placebo (n=265). Only 13% of placebo patients and 17% of lisinopril patients had microalbuminuria (AER 20-200 μg/min) whereas 40% had been assumed for statistical power calculations.

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. When adjusted for BP, the difference was reduced to 17.3% (p=0.05). 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. No significant difference between the treatment groups was found in the relative % difference in AER although there was a tendency in favour of lisinopril.

When the treatment effect was stratified according to baseline AER using four categories: <5, 5-<10, 10-<20 and 20-200 μg/min, statistical difference was not reached in any of these categories. 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**.** At 24 months, the treatment difference in mean AER between lisinopril and placebo was 0.23 μg/min in patients who were normoalbuminuric at baseline (p=0.6), compared with a difference of 38.5 μg/min for patients who were microalbuminuric at baseline (p=0.001).

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.

Trial 298 A multicentre study to compare the effects on urinary albumin excretion rate and blood pressure of lisinopril and nifedipine SR in hypertensive NIDDM (type 2) diabetic patients with incipient nephropathy (BRILLIANT).

This was a double blind, randomised, parallel-group trial of lisinopril (n=168) versus nifedipine slow release (n=167) on AER and BP control in 59 European centres.

Lisinopril-treated patients were shown to have a 20 µg/min larger reduction in the median of AER, compared with nifedipine SR-treated patients at both 6 (p=0.0002)and 12 months (p=0.0006). However, no difference was found in creatinine clearance between treatment groups.

In addition to the BRILLIANT study, data was provided from another trial (CALM; BMJ 2000; 321: 1440-1444), a prospective multicentre, double blind parallel group study where lisinopril was compared with candesartan and a combination of lisinopril and candesartan.

At 12 weeks urinary albumin: creatinine ratios were 30% (15% to 42%, P<0.001) and 46% (35% to 56%, P<0.001) for candesartan and lisinopril, respectively. At 24 weeks the reduction in urinary albumin: creatinine ratio with combination treatment (50%, 36% to 61%, P<0.001) was greater than with candesartan (24%, 0% to 43%, P=0.05) and lisinopril (39%, 20% to 54%, P<0.001).

Safety in EUCLID and BRILLIANT studies

Adverse events reported in the trials were as expected in the patient population or known with ACE inhibitors and the trials provided reassuring evidence that glycaemic control was not significantly altered by lisinopril in any direction.

Overall conclusions

It is accepted that treatment with ACE inhibitors is established first-line therapy in patients with IDDM and any degree of hypertension.

The EUCLID study was ill suited to provide support for the proposed indication. 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 pre-defined analyses

The BRILLIANT and CALM studies in hypertensive NIDDM patients used the surrogate end-point of a decrease in microalbuminuria, instead of more clinically relevant outcomes such as GFR or dialysis. However, in the patient population studied it would be difficult to distinguish changes in GFR between groups. Thus, a significant delay in the more surrogate end-point "progression to macroalbuminuria" is considered clinically relevant despite the absence of a positive effect on GFR. There is also strong external support for the benefit of RAAS modulation which makes a restricted indication in patients with NIDDM and hypertension reasonable.

The CPMP considered that the data did not support the indication in normotensive IDDM patients but that the indication in hypertensive NIDDM patients could be granted.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the CPMP considered the referral made under article 7(5) of Commission Regulation EC No 541/95, for Cardiostad (lisinopril) and associated names (see Annex I),
- the CPMP agreed that Cardiostad (lisinopril) is effective in the indication :

  Renal Complications of Diabetes Mellitus
  Treatment of renal disease in hypertensive patients with type 2 diabetes mellitus and incipient nephropathy.

- no unexpected adverse events related to the proposed extended indication were found.
- The CPMP, as a consequence, considered the benefit/risk balance for the above-mentioned additional indication to be favourable,

The CPMP has recommended the granting of the variation of the Marketing Authorisation for which the Summary of Product Characteristics is set out in Annex III for Cardiostad (lisinopril) and associated names (see Annex I).

ANNEX III

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

Note: This SPC is the one that was annexed to the Commission Decision on this Article 7(5) referral for Cardiostad (Lisinopril) and related names. 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

<invented name> 5 mg tablets
<invented name> 10 mg tablets
<invented name> 20 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 5.44 mg lisinopril dihydrate equivalent to 5 mg lisinopril
One tablet contains 10.89 mg lisinopril dihydrate equivalent to 10 mg lisinopril
One tablet contains 21.7 8 mg lisinopril dihydrate equivalent to 20 mg lisinopril

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets
The 5 mg tablets are white, round, biconvex, with imprint '5' on one side and scored on both sides.
The 10 mg tablets are white, round, biconvex, with imprint '10' on one side and quadrisected on both sides.
The 20 mg tablets are white, round, biconvex, with imprint '20' on one side and quatrisected on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Arterial hypertension.
  It may be used alone or concomitantly with other classes of antihypertensive agents, e.g. thiazide diuretics.

- Treatment of heart failure as additive therapy to non-potassium sparing diuretic, and where appropriate, digitalis.

- Treatment of acute myocardial infarction, in haemodynamically stable patients (systolic blood pressure > 100 mmHg) without significant renal dysfunction (serum creatinine < 177 micromol/l [2.0 mg/dl] and proteinuria < 500 mg/24 hours). Lisinopril should be given in additon to usual standard therapy in MI (thrombolytics, acetylsalicylic acid and ß blocking agents), especially together with nitrates

- Renal Complications of Diabetes Mellitus
  Treatment of renal disease in hypertensive patients with type 2 diabetes mellitus and incipient nephropathy.'

4.2 Posology and method of administration

Precautionary note:
Excessive first dose hypotension may occur in high risk patients (in patients with salt and/or fluid deficiency, e.g. after dialysis, vomiting, diarrhoea, in concomitant diuretic therapy, in patients with heart failure, severe or renal hypertension). Initiation of therapy requires, if possible, correction in salt and/or body fluids deficiencies, discontinuation or reduction of an existing diuretic therapy for two to three days before starting ACE inhibition and starting therapy with the lowest single dose of 2.5 mg lisinopril in the morning.
Patients at high risk for severe acute hypotension should be monitored medically preferably in hospital, for as long as its maximal effect is expected (generally for at least 8 hours) after administration of the first dose and whenever the dose of ACE inhibitors and/or diuretic is increased. This also applies to patients with angina pectoris or cerebrovascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident.
In patients with malignant hypertension or severe cardiac insufficiency initiation of therapy and dose adjustment should be performed in a hospital.
Unless prescribed otherwise, the following dosage regimen is recommended:

Arterial hypertension
Treatment should be initiated with 5-10 mg in the morning.
The dose should be titrated to give optimum control of blood pressure. The time interval between dose increases should not be less than 3 weeks.
The usual maintenance dose is 20 mg lisinopril once daily, but doses up to 80 mg once daily may be used.

A lower initial dose (2.5 mg lisinopril in the morning) will be necessary at renal impairment, at heart failure, in patients who do not tolerate discontinuation of diuretic treatment, in patients who are volume and/or salt depleted (e.g. after vomiting, diarrhoea or diuretic therapy), in patients with severe or renovascular hypertension and in elderly patients.

Heart failure
Lisinopril can be given in addition to existing therapy with diuretics and digitalis.
The initial dose is 2.5 mg lisinopril in the morning. The maintenance dose should be titrated in increments of 2.5 mg lisinopril at intervals of two to four weeks.
Dose increases must be gradual and reflect individual patient response to therapy.
The usual maintenance dose is 5-20 mg once daily. The maximum dose of 35 mg lisinopril per day should not be exceeded.

Acute myocardial infarction in haemodynamically stable patients
Lisinopril should be given as supplement to the usual standard therapy in MI. Treatment with lisinopril may be initiated within 24 hours of symptom onset provided that the patients are haemodynamically stable. The initial dose is 5 mg lisinopril and then 5 mg after 24 hours, 10 mg after 48 hours and thereafter 10 mg once daily. Patients with low systolic blood pressure (120 mmHg or lower) at the start of treatment or during the first 3 days following the infarction, should be treated with a lower dose – 2.5 mg (see section 4.4). In case of hypotension (systolic blood pressure lower than 100 mmHg), a daily maintenance dose of 5 mg should not be exceeded, with reduction to 2.5 mg if necessary. If hypotension persists (systolic blood pressure lower than 90 mmHg for more than 1 hour) despite of a dose reduction to 2.5 mg lisinopril per day, lisinopril should be discontinued.
The treatment should be continued for 6 weeks. The minimal maintenance dose is 5 mg lisinopril per day.
Patient with symptoms of cardiac insufficiency should continue treatment with lisinopril (see section 4.2).
Lisinopril is compatible with intravenous or transderma administration of glyceryl nitrate.

Dosage in moderate renal impairment
If the creatinine clearance is 30-70 ml/min respectively, and in elderly patients (over 65 years):

The initial dose is 2.5 mg lisinopril in the morning, the maintenance dose is usually 5-10 mg lisinopril per day according to blood pressure control. The maximum dose of 20 mg lisinopril per day should not be exceeded.

It is recommended discontinuing administration of diuretics 2 or 3 days before initiation of therapy with lisinopril. The possibility of hypotensive effects with lisinopril can be minimised by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with lisinopril.

Children
Efficacy and safety of use in children has not been established. Therefore use in children is not recommended.

Renal complications of diabetes mellitus
In hypertensive patients with type 2 diabetes mellitus, the dose is 10mg lisinopril once daily which should be increased to 20mg once daily, if necessary, to achieve a sitting diastolic blood pressure below 90mm Hg.

Lisinopril can be taken independently from meals, but should be taken with a sufficient amount of liquid.
Lisinopril should be administered once daily.
Place the <invented name> snaptab on a hard surface with the centre groove facing upward. Exert pressure from the top with your thumb and the snaptab will break into two equal pieces.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients or other ACE inhibitors
- History of angioneurotic oedema related to previous ACE-inhibitor treatment hereditary/idiopathic angioneurotic oedema (see section 4.4.)
- severe renal impairment (creatinine clearance < 30 ml/min)
- haemodynamically relevant aortic or mitral valve stenosis or hypertrophic cadiomyopathy
- in haemodynamically unstable patients after acute myocardial infarction
- systolic blood pressure ≤ 100 mmHg before initiation of the treatment with lisinopril
- lactation period
- pregnancy (see sexction 4.6)
- Concurrent use of lisinopril and poly(acrylonitrile, sodium-2-methylallyl-sulphonate)highflux membranes for emergency dialysis bears the risk of anaphylactic reactions (hypersensivity reactions to the point of shock). This combination must therefore be avoided either by using other drugs (but not ACE inhibitor) for the treatment of hypertension and/or heart failure, or by using other membrane for dialysis. (see section 4.4).
- cardiogenic shock

4.4 Special warnings and special precautions for use

Patients on multiple or high-dose diuretics (>80 mg of frusemide) with hypovolaemia, hypontraemia (serum sodium <130 mmol/l) pre-existing hypotension, unstable cardiac failure, renal impairment, high-dose vasodilator therapy and patients age 70 years or over are recommended to have lisinopril therapy initiated in hospital.

Hypotension
Lisinopril may cause a profound fall in blood pressure especially after the first dose.
Symptomatic hypotension is rare in uncomplicated hypertensive patients. It is more likely to occur in patients who have been electrolyte- or vole-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting. It has been reported mainly in patients with severe heart failure with or without associated renal insufficiency. This is more likely in patients on high doses of loop diuretics, or those with hyponatreamia or functional renal impairment. In these patients treatment should be started under close medicinal supervision preferably in hospital, with low doses and careful dose titration with simultaneous

control of renal function as well as serum potassium levels. If possible, diuretic treatment should be discontinued temporarily. Such considerations apply also to patients with angina pectoris or cerebrosvascular disease in whom excessive hypotension could result in a myocardial infarction or cerebrovascular accident. If hypotension develops the patient should be placed in supine position and volume repletion with oral or intravenous fluids may be required. Atropine may be necessary for treatment of associated bradycardia. The appearance of hypotension after initial dose does not preclude subsequent careful dose titration with medicinal product after effective treatment. If non-acute hypotension in patients with heart failure becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or lisinopril may become necessary.
If possible, diuretic therapy should be discontinued for 2-3 days prior to initiation of lisinopril.

Hypotension in acute myocardial infarction
Treatment with lisinopril must not be initiated in acute myocardial infarction patients if there is a risk of additional serious haemodynamic exacerbation following treatment with a vasodilator. These are patients with a systolic blood pressure of 100 mmHg or lower or with cardiogenic shock. The maintenance dose should be reduced to 5 mg or temporarily to 2.5 mg, in case the systolic blood pressure is 100 mmHg or lower. Treatment with lisinopril in acute myocardial infarction patients may lead to severe hypotension. In persisting hypotension (systolic blood pressure < 90 mmHg for more than 1 hour), lisinopril should be discontinued.

In patients with severe heart failure following an acute myocardial infarction lisinopril should only be administered if the patient is haemodynamically stable.

Renovascular hypertension / Renal artery stenosis
There is an increased risk for severe hypotension and renal insufficiency when patients with renovascular hypertension and pre-existing bilateral renal artery stenosis or stenosis of the artery to a solitary kidney are treated with lisinopril. Treatment with diuretics may be a contributory factor. Loss of renal function may occur with only mild changes in serum creatinine even in patients with unilateral renal artery stenosis. In these patients treatment should be started in hospital under close medical supervision with low doses and careful dose titration. Diuretic treatment should be discontinued and renal function monitored during the first weeks of therapy.

Impaired renal function
In patients with severe renal failure (creatinine clearance <30 ml/min) the use of lisinopril is contra-indicated (see section 4.3).
Lisinopril should be used with caution in patients with renal insufficiency who may require reduced or less frequent doses (see section 4.2).
Changes in renal function may be anticipated in susceptible individuals due to the inhibition of the renin-angiotensin-aldosterone system. Close monitoring of the renal function during therapy should be performed as deemed appropriate in those with renal insufficiency. Renal failure has been reported in association with lisinopril mainly in patients with severe heart failure or underlying renal disease including renal artery stenosis. If recognised promptly and treated appropriately, renal failure when associated with lisinopril treatment is usually reversible.
Some hypertensive patients with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when lisinopril has been given concurrently with a diuretic. This situation should lead to reduction of dose/discontinuation of lisinopril/diuretics and raise the possibility of underlying renal artery stenosis.
In acute myocardial infarction treatment with lisinopril should not be initiated in patients with signs of renal impairment, defined as a serum creatinine concentration ≥ 177 micromol/l (2.0 mg/dl) and/or proteinuria above 500 mg/day. If renal impairment develops during treatment with lisinopril (serum creatinine clearance <30ml/min, or a doubling of the pre-treatment creatinine value), lisinopril must be discontinued.

There is limited experience of lisinopril in renal transplant recipients. Treatment with lisinopril is therefore generally not recommended for the category of patients.

Haemodialysis
In patients in permanent haemodialysis the use of lisinopril is contra-indicated (see section 4.3). Concomitant application of lisinopril and poly(acrylonitrile, sodium-2-methylallyl-sulphonate) high-flux membranes during dialysis or haemofiltration carries a risk of anaphylactic reactions (hypersensitivity reactions up to anaphylactic shock). First indications of this anaphylaxis are swelling of the face, redness, hypotension and dyspnoea within a few minutes of commencing haemodialysis. It is recommended to use an alternative membrane in dialysis or an alternative antihypertensive drug in the treatment of hypertension or heart failure (see section 4.3).

Hyperkalemia
Hyperkalemia may occur during treatment with lisinopril, especially in the presence of renal insufficiency and/or heart failure. Potassium supplements or potassium sparing diuretics are generally not recommended, since they may lead to significant increases in serum potassium. If concomitant use of the above mentioned agents is deemed appropriate, they should be used with frequent monitoring of serum potassium.

Primary hyperaldesteronism
Patients with primary hyperaldosteronism generally do not respond to antihypertensives with a mode of action based on inhibition of the renin-anigotensin-system. The use of lisinopril is, therefore, not recommended.

Proteinuria
In patients with existing renal function impairment or on relatively high doses of lisinopril rarely proteinuria may occur. In patients with clinically relevant proteinuria (more than 1 g/day) lisinopril should be given after very critical assessment of the risk versus benefit and with regular monitoring of clinical and laboratory parameters.
Elderly
Some elderly patients may be more responsive to an ACE inhibitor than younger patients. In patients older than 65 years administration of low initial doses (2.5 mg lisinopril) and monitoring of blood pressure, evaluation of renal function and/or representative laboratory parameters in the initial phase of therapy is recommended.

LDL-lipid apheresis / Desensitisation therapy
During LDL (low-density lipoprotein) apheresis with dextran sulphate, life-threatening anaphylactic reactions may occur when ACE-inhibitor is administered.
Life-threatening anaphylactic reactions (e.g. blood pressure decrease, breathlessness, vomiting, allergic skin reactions) may also occur during desensitisation therapy for insect venom (e.g. bee, wasp stings) and concurrent use of lisinopril.
If LDL apheresis or desensitisation therapy for insect venom is necessary, lisinopril should be temporarily replaced by different drugs (other ACE inhibitors excluded) for hypertension or heart failure.

Angioneurotic oedema (see section 4.3)
Angioneurotic oedema of the face, extremities, lips, mucous membranes**,** tongue, glottis and/or larynx rarely have been reported in patients treated with ACE-inhibitors including lisinopril which especially occurs during the first weeks of treatment. However, in rare cases angioedema may develop after longterm treatment with an ACE-inhibitor. In such cases, lisinopril therapy should be discontinued promptly and an appropriate monitoring of the patient has to be instituted.

In cases where swelling has been confined to the face and lips, the condition generally resolves without treatment although antihistamines have been useful in relieving symptoms. Patients with a known history of angioedema unrelated to ACE-inhibitor therapy may have an increased risk for developing angioedema after taking an ACE-inhibitor. Angioedema involving the tongue, glottis and/or larynx can be fatal. Emergency therapy should be initiated, including, but not necessarily limited to immediate subcutaneous injection of 0.3-0.5 mg epinephrine or slow intravenous administration of 0.1 mg epinephrine (dilution instructions to be observed) with ECG and blood pressure monitoring. Patients have to be hospitalised. Suitable monitoring

should be initiated over a minimum of 12 to 24 hours in order to ensure complete resolution of the symptoms before the patient is discharged from hospital.
ACE-inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Aortic stenosis / Hypertrophic cardiomyopathy
ACE inhibitors should be used with caution in patients with left ventricular outflow tract obstructions. If the obstruction is haemodynamically relevant, lisinopril is contra-indicated.

Neutropenia/Agranulocytosis
The risk of neutropenia appears to be dose-and-type related and is dependent on patient's clinical status. Neutropenia and agranulocytosis rarely have been observed in hypertensive patients treated with ACE-inhibitors. It is rarely seen in patients with uncomplicated hypertension but were more common in patients with renal impairment especially if associated with collagen vascular disease (e.g. systemic lupus erythematosus or scleroderma) or concurrent treatment with immunosuppressive agents. Regular white cell counts should be obtained in those patients.
Neutropenia and agranulocytosis are reversible after withdrawal of the ACE inhibitor.

Cough
Cough has been reported with the use of ACE inhibitors. It is characteristically non-productive, persistent and resolves after discontinuation of therapy.

Surgery/anaesthesia
Lisinopril blocks angiotensin II formation secondary to compensatory renin release in patients undergoing major surgery or anaesthesia with agents that produce hypotension. Resultant hypotension can be corrected by volume expansion (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics
When a diuretic is administered concomitantly with lisinopril treatment, the antihypertensive effect is generally additive.

Patients already in treatment with diuretics and especially those patients, whom the diuretic has been instituted recently, may occasionally experience a fall in blood pressure when lisinopril is added to the therapy. The risk of symptomatic hypotension during treatment with lisinopril can be reduced by discontinuing the diuretic prior to starting <invented name> (see section 4.4 and section 4.2).

Potassium-sparing diuretics or potassium supplements
Additive potassium-enhancing effects can occur with potassium-sparing diuretics, particularly in patients with renal impairment.
ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, triamterene, or amiloride, potassium supplements or potassium containing salt substitutes may lead to significant increases in serum potassium.. If concomitant use is indicated because of documented hypokalemia they should be used with caution and with frequent monitoring of serum potassium.

Sodium chloride
Reduces the blood pressure lowering and heart failure symptom improving effect of lisinopril.

Antihypertensive agents
Increase the blood pressure lowering effect of lisinopril, especially with diuretics.

Anagelsic and anti-inflammatory agents
(e.g. acetylsalicylic acid, indomethacin): may reduce the blood pressure lowering effect of lisinopril.

Lithium
As with therapy involving other drugs that promote sodium excretion, lithium clearance may be lowered. Serum lithium levels should therefore be monitored carefully if lithium salts are to be administered. The posology should be adapted when necessary**.**

Alcohol
ACE inhibitors increase the effect of alcohol. Alcohol enhances the hypotensive effects of ACE inhibitors.

Anaesthetics / narcotics / hypnotics
Greater blood pressure fall (so the anaesthetist has to be informed of lisinopril therapy).

Sympathomimetics
May reduce the antihypertensive effects of ACE inhibitors.
An increased risk of leucopenia has been noted with the concomitant administration of allopurinol, cytostatic or immunosuppressive agents, systemic corticosteroids or procaiamide.

Oral antidiabetics (e.g. sulphonyl urea drugs/biguanides), insulin
ACE inhibitors may enhance the hypoglycaemic effects of antidiabetic medication, particularly during the first weeks of combined treatment.

Antacid:
May reduce the bioavailability of ACE inhibitors.

Non-steriodal anti-inflammatory drugs
The administration of a non-steroidal anti-inflammatory agent may reduce the antihypertensive effect of lisinopril. Lisinopril exerts an additive effect on the increase of serum potassium, whereas renal function may decrease. These effects are in principle reversible, and occure especially in patients with comprised renal function.

4.6 Pregnancy and lactation

Pregnancy
The use of lisinopril during pregnancy is contraindicated (see section 4.3)

Appropriate and well-controlled studies have not been done in humans. ACE inhibitors cross the placenta and can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

Fetal exposure to ACE inhibitors during the second and third trimesters has been associated with neonatal hypotension, renal failure, face or skull deformities and/or death. Maternal oligohydramnios has also been reported reflecting decreasing renal function in the fetus. Limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios. Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. Oliguria should be treated with support of blood pressure and renal perfusion.

Intrauterine growth retardation, prematurity, patent ductus arteriosus and fetal death have also been reported but it is not clear whether they are related to the ACE inhibition or the underlying maternal disease.

It is not known whether exposure limited to the first trimester can adversely affect fetal outcome. Women who become pregnant while receiving lisinopril should be informed of the potential hazard to the fetus.

Lactation
ACE inhibitors may excreted in breast milk and their effect on the nursing infant has not been determined. It is recommended that lactating mothers should not breast feed while taking lisinopril.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

The following undesirable effects have been observed in association with lisinopril therapy or with other ACE inhibitors:

Cardiovascular system
Occasionally, severe hypotension may occur after initiation of therapy or with increase of the dosage of lisinopril and/or diuretics. This occurs especially in certain risk groups, e.g. in patients suffering from salt or fluid deficiency after diuretic therapy, heart failure and severe or renal hypertension. Symptoms like dizziness, feeling of weakness, impaired vision, rarely accompanied by loss of consciousness (syncope), can occur.
Individual cases of tachycardia, palpitations, arrhythmia, chest pain, angina pectoris, myocardial infarction, transient ischemic attacks and stroke have been reported for ACE inhibitors in association with pronounced blood pressure fall.

If lisinopril is administered in acute myocardial infarction patients, occasionally – especially within the first 24 hours – second or third degree AV block and/or severe hypotension and/or renal impairment, in rare cases cardiogenic shock, may occur.

Kidneys
Renal insufficiency may occur or be intensified. Acute renal failure has been reported in single cases. Proteinuria, partly with simultaneous deterioration of renal function, has been observed.

Respiratory system
Occasionally, dry cough, sore throat, hoarseness and bronchitis, rarely dyspnoea, sinusitis, rhinitis, bronchospasm/asthma, pulmonal infiltration, stomatitis, glossitis and dry mouth may occur. In individual cases angioneurotic oedema involving the upper airways has caused fatal airway obstruction (see section 4.4.).
Isolated cases of allergic alveolitis (eosinophilic pneumonia) have been described in relation to therapy with lisinopril.

Gastro-intestinal tract / liver
Occasionally nausea, abdominal pain and indigestion, rarely vomiting, diarrhoea, constipation and loss of appetite can occur.
ACE inhibitors have rarely been associated with a syndrome of cholestatic jaundice, fulminant hepatic necrosis, and death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice the ACE inhibitor should be stopped and the patient should be monitored medically.
In patients receiving ACE inhibitors individual cases of hepatic dysfunction, hepatitis, liver insufficiency, pancreatitis and ileus have been described in relation to therapy with ACE inhibitors.

Skin, vessels
Occasionally allergic skin reactions like rash can occur, rarely pruritus, urticaria as well as angioneurotic oedema of the face, lips and/or limbs.
In isolated cases sever skin reactions like pemphigus, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been described. Skin reactions can be accompanied by fever, myalgia, arthralgia, vasculitis, eosinophilia, leucocytosis and/or increased ANA-tires.
In case of suspected serious skin reaction the attending physician has to be consulted immediately and therapy with lisinopril needs to be terminated.

Individual cases of psoriasis-like skin changes, photosensitivity, flush, diaphoresis, alopecia, onycholysis and exacerbation of Raynaud's disease have been observed with ACE inhibitor therapy.

Nervous system
Occasionally headache and tiredness, rarely somnolence, depressions, sleep disorders, impotence, peripheral neuropathy with paraesthesia, disorders of balance, muscle cramps, nervousness, confusion, tinnitus, blurred vision, taste disturbances and temporary loss of taste.

Laboratory parameters (blood, urine)
Occasionally haemoglobin, haematocrit, white cell count or platelets may be decreased. There have been rare reports of anaemia, thrombocytopenia, neutropenia or eosinophilia, and isolated reports of agranulocytosis or pancytopenia, especially in patients with impaired renal function, collagen disease or concurrent treatment with allopurinol, procainamide or certain immunosuppressive drugs.
In patients with a congenital deficiency concerning G-6-PDH individual cases of haemolytic anaemia have been reported.
Increases in serum creatinine, urea and potassium respectively decrease in serum sodium concentration may rarely occur, especially in the presence of renal insufficiency, severe heart failure and renovascular hypertension. In patients with diabetes mellitus hyperkalemia have been observed.
Proteinuria may be increased in special cases (see section 4.4).
Elevation of liver enzymes and serum billirubin have been reported in isolated cases.

Special remarks
The above mentioned laboratory parameters should be performed before and regularly during treatment with lisinopril.
Especially in the initial phase of treatment and in high-risk patients (patients with renal insufficiency, in collagen disease) as well as concurrent treatment with immunosuppressive or cytostatic agents, allopurinol and procainamide, serum electrolyte and serum creatinine concentrations as well as full blood count should be monitored.
Patients experiencing such symptoms as fever, lymph node swelling and/or sore throat in the course of lisinopril therapy should have a white cell count without delay.

4.9 Overdose

No case of overdose has been reported.
The most likely overdosage phenomenon would be severe hypotension, shock, bradycardia, electrolyte disturbances and renal failure, the normal treatment being an infusion with a standard saline solution.
Lisinopril can be eliminated from the blood by haemodialysis.

After ingestion of an overdose, the patients should be kept under close supervision, preferably in an intensive care unit. Serum electrolytes and creatinine should be monitored frequently. Precautions should be taken against absorption such as gastric lavage, administration of absorbents or sodium sulphate Should be instituted within 30 minutes of intake. Measures to hasten elimination may also be taken. If hypotension occurs, the patient should be placed in shock position and intravenously salt and volume supplementation should be given rapidly. Treatment with angiotensin II should be considered. Bradycardia should be treated by administering atropine. The use of pacemaker may be considered. ACE inhibitors may be removed from the circulation by haemodialysis. The use of high-flux polyacrylonitrile membranes should be avoided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors, ATC code: C 09 AA 03

Lisinopril is an angiotensin converting enzyme inhibitor. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance angiotensin II. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreases aldosterone secretion.
ACE is identical with kininase II. Thus lisinopril may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of lisinopril remains to be elucidated.

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.

5.2 Pharmacokinetic properties

The bioavailability of lisinopril is about 29% with an inter-patient variation of 6-60%. Maximum plasma concentrations are reached within approximately 7 hours after oral administration. Food does not affect the rate or extent of absorption.

Lisinopril is not metabolised and the absorbed fraction is excreted completely unchanged in urine. Following multiple dosing, lisinopril displayed an effective half-life of 12.6 hours. Most of the drug is eliminated during the earlier phase, which does not contribute to drug accumulation. The terminal phase probably represents a saturable binding to ACE and is not proportional to the dose. Lisinopril does not appear to bind to other plasma proteins than ACE.

Acute myocardial infarction patients tend to have a slightly longer time to peak concentrations. Impaired renal function reduces the excretion of lisinopril through the kidneys. Elderly patients have higher AUC values than younger patients. Dosage adjustment is recommended in patients with creatinine clearance <70 ml/min and in elderly (see section 4.2). Lisinopril can be removed by dialysis.

5.3 Preclinical safety data

Lisinopril dihydrate is safe with regard to genotoxicity. 2-years carcinogenicity studies in rats and mice failed to show any evidence of carcinogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate, dihydrate
Silica colloidal anhydrous
Magnesium stearate
Maize starch
Mannitol
Maize starch pregelatinised

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/aluminium blisters containing
14, 20, 28, 30, 50, 56, 60, 98, 100, 150, 200, 300, 400, 500 or 1000 tablets

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<To be completed as appropriate.>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed as appropriate.>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<To be completed as appropriate.>

10. DATE OF REVISION OF THE TEXT

<To be completed as appropriate.>