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

September 2003
CPMP/886/04/Final

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

Lisinopril Biochemie

International non-proprietary name (INN): Lisinopril

BACKGROUND INFORMATION

Lisinopril Biochemie, 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 Lisinopril Biochemie applied to the Reference Member State (Denmark) for a variation through the Mutual Recognition Procedure to add an indication: "treatment of incipient nephropathy." 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 incipient nephropathy indication and since Lisinopril Biochemie 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 25th July 2002, the Netherlands referred the matter to the CPMP.

The referral procedure started on 20 September 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 9 January 2003, 27 June 2003 and 11 July 2003.

Based on evaluation of the currently available data and the Rapporteurs' assessment reports, the CPMP considered that the data did not support an 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.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.eu.int http://www.emea.eu.int

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	Tyrol Pharma GmbH, Biochemiestrasse 10, Kundl, Austria	LISINOTYROL	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 60, 98, 100, 100x1, 500 tablets
Austria	Tyrol Pharma GmbH, Biochemiestrasse 10, Kundl, Austria	LISINOTYROL	10 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28, 30, 100, 100x1, 250 tablets
Austria	Tyrol Pharma GmbH, Biochemiestrasse 10, Kundl, Austria	LISINOTYROL	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 98, 100, 100x1, 250, 500 tablets
Belgium	Biochemie N.V., Medialaan 40, Vilvoorde, Belgium	Lisinopril BC	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30 56, 60, 98, 100, 100x1, 250, 500 tablets
Belgium	Biochemie N.V., Medialaan 40, Vilvoorde, Belgium	Lisinopril BC	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 98, 100, 100x1, 250, 500 tablets
Denmark	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 60, 98, 100 x 1, 100, 250, 500 tablets
Denmark	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	10 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28, 30, 100, 100 x 1, 250 tablets
Denmark	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 98, 100, 100 x 1, 250, 500 tablets

Member State	Marketing Authorisation Holder	(Invented) Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Finland	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 60, 98, 100 x 1, 100, 250, 500 tablets in blister 14, 28, 30, 56, 60, 98, 100, 250, 500 tablets in container
Finland	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	10 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28, 30, 100, 100 x 1, 250 tablets in blister 28, 30, 100, 250 tablets in container
Finland	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 98, 100, 100 x 1, 250, 500 tablets in blister 14, 28, 30, 56, 98, 100, 250, 500 tablets in container

Member State	Marketing Authorisation Holder	(Invented) Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Luxembourg	Biochemie N.V., Medialaan 40, Vilvoorde, Belgium	Lisinopril BC	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28, 56 tablets
Luxembourg	Biochemie N.V., Medialaan 40, Vilvoorde, Belgium	Lisinopril BC	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28, 56 tablets
The Netherlands	Multipharma B.V., Gemeenschapspolderweg 28, NL-1382 Weesp, The Netherlands	MP-Lisinopril	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 60, 98, 100, 250, 500 tablets
The Netherlands	Multipharma B.V., Gemeenschapspolderweg 28, NL-1382 Weesp, The Netherlands	MP-Lisinopril	10 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28, 30, 100, 250 tablets
The Netherlands	Multipharma B.V., Gemeenschapspolderweg 28, NL-1382 Weesp, The Netherlands	MP-Lisinopril	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 98, 100, 250, 500 tablets
Portugal	Biochemie GmbH, Biochemiestrasse 10, A-6250 Kundl, Austria	Lisinopril Biochemie	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 60, 98, 100, 500, 100 x 1 (blister only) tablets
Portugal	Biochemie GmbH, Biochemiestrasse 10, A-6250 Kundl, Austria	Lisinopril Biochemie	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 98, 100, 100 x 1 (blister only), 250, 500 tablets

Member State	Marketing Authorisation Holder	(Invented) Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Spain	Laboratorios Géminis S.A., Gran Via de les Corts Catalanes 764, Barcelona, Spain	Lisinopril Géminis	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	60, 500 tablets
Spain	Laboratorios Géminis S.A., Gran Via de les Corts Catalanes 764, Barcelona, Spain	Lisinopril Géminis	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28, 500 tablets
Sweden	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 60, 98, 100, 250, 500 tablets
Sweden	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	10 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 60, 98, 100, 250, 500 tablets
Sweden	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	14, 28, 30, 56, 60, 98, 100, 250, 500 tablets
United Kingdom	Multipharma B.V., Gemeenschapspolderweg 28, NL-1382 Weesp, The Netherlands	Lisinopril	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28 tablets
United Kingdom	Multipharma B.V., Gemeenschapspolderweg 28, NL-1382 Weesp, The Netherlands	Lisinopril	10 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28 tablets
United Kingdom	Multipharma B.V., Gemeenschapspolderweg 28, NL-1382 Weesp, The Netherlands	Lisinopril	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	28 tablets

Member State	Marketing Authorisation Holder	(Invented) Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Norway	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	5 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	30, 100, 250 tablets
Norway	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	10 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	30, 100, 250 tablets
Norway	Biochemie GmbH, Biochemiestrasse 10, Kundl, Austria	Lisinopril Biochemie	20 mg	Tablet	Oral use	Blisters (PVC/Alu)and Bottles (PP)	100, 250 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 LISINOPRIL BIOCHEMIE 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 Lisinopril Biochemie applied to the Reference Member State (RMS) for a variation through the Mutual Recognition Procedure to add an indication; "treatment of incipient nephropathy." 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 Denmark which is the RMS for Lisinopril Biochemie. 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 has the indication "incipient nephropathy in diabetes characterised by microalbuminuria." Since Lisinopril Biochemie 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 Lisinopril Biochemie and associated names (see Annex I),

- the CPMP agreed that Lisinopril Biochemie 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 Lisinopril Biochemie 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 Lisinopril Biochemie 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 mg, 10 mg or 20 mg lisinopril, respectively, as lisinopril dihydrate

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Tablets

The 5 mg tablets are white, round, uncoated, biconvex with a diameter of 8 mm and a score
The 10 mg tablets are light pink, round, uncoated, biconvex with a diameter of 7 mm and a score
The 20 mg tablets are pink, round, uncoated, biconvex with a diameter of 9 mm and a score

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment of heart failure in combination with non-potassium-sparing diuretics, and if necessary with digitalis.

Treatment of acute myocardial infarction, within 24 h at the onset of AMI, in hemodynamic stable patients (systolic blood pressure > 100 mmHg, serum creatinine < 177 micromol/L(2.0 mg/10 mL) and proteinuria < 500 mg/24 h).

Lisinopril should be administered as supplement to usual standard treatment of myocardial infarction (nitrates, thrombolytics, acetylsalicylic acid and ß blocking agents)

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

Caution:
Distinct first dose hypotension may occur in the high-risk group of patients (volume and/or salt depleted patients, i.e. after dialysis, vomiting, diarrhoea, or at concomitant treatment with diuretics, patients with heart failure, severe hypertension or renovascular hypertension). Salt and/or volume depleted patients should if possible have these conditions corrected before treatment is initiated, possible diuretics should be

discontinued, or the dose should be reduced for 2 to 3 days before treatment with ACE-inhibitors, and the treatment should be initiated with the lowest single dose of 2.5 mg lisinopril in the morning.

At high risk of severe acute hypotension, the patient should be supervised closely by a physician, preferably in a hospital, for the time corresponding to the expected maximum effect after administration of the first dose (usually minimum 8 hours), and every time the dose of ACE-inhibitor and/or diuretic is increased. This applies also for patients with angina pectoris or cerebrovascular disease, where a big fall in blood pressure may cause myocardial infarction or cerebral thrombosis.

In patients suffering from malignant hypertension or severe heart disease, the treatment and the dose adjustment should be performed in a hospital.

Unless otherwise prescribed, the following dosage is recommended:

Arterial hypertension
The recommended initial dose is 5 – 10 mg in the morning. The dose should be titrated until the maximum control of the blood pressure has been achieved. The time interval between dose increases should be at least 3 weeks.

Usual maintenance dose is 20 mg lisinopril once daily, but doses up to 80 mg once daily can be used.

A lower initial dose (2.5 mg lisinopril in the morning) is necessary at decreased renal funktion, at heart failure, in patients who do not tolerate discontinuation of diuretics, in patients who are volume and /or salt depleted (i.e. after vomiting, diarrhoea or treatment with diuretics), in patients with severe or renovascular hypertension and in elderly.

Heart failure
Lisinopril can be administered as supplement to an ongoing treatment with diuretics and digitalis.

Initial dose is 2.5 mg lisinopril in the morning. Maintenance dose should be titrated stepwise with an increase of 2.5 mg every time.

The increase of the dose should be dependent of the response of the patient to the treatment. The time interval between dose increases should be at least 2 weeks and preferably 4 weeks. The usual maintenance dose is 5-20 mg once daily

The maximum daily dose of 35 mg lisinopril should not be exceeded.(see precautionary note above)

Acute myocardial infarction
Lisinopril should be administered as supplement to a general standard treatment of myocardial infarction.

Treatment with lisinopril can be initiated within 24 hours after occurrence of the symptoms, provided that the patient is hemodynamic stable. Initial dose is 5 mg lisinopril and hereafter 5 mg after 24 hours, 10 mg after 48 hours, and hereafter 10 mg once daily. Patients with low systolic blood pressure (120 mmHg or lower) at the beginning of treatment or during the first 3 days after 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 maximum 5 mg can be administered, possibly with a reduction to 2.5 mg. If the hypotension persists (systolic blood pressure lower than 90 mmHg for more than 1 hour) despite dose reduction to 2.5

mg lisinopril daily, lisinopril should be discontinued.

The treatment should be continued for 6 weeks. The lowest maintenance dose is 5 mg lisinopril daily. Patients with symptoms of heart failure should continue the treatment (see section 4.4).

Lisinopril is compatible with intravenous or transdermal administration of nitroglycerine.

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

Dosage in moderate renal impairment
Creatinine clearance of 30 to 70 mL/min and in elderly patients (above 65 years):
Initial dose is 2.5 mg lisinopril in the morning.

Usual maintenance dose is 5 to 10 mg lisinopril daily dependent on the respons of blood pressure.

The maximum dose of 20 mg lisinopril daily 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.

Lisinopril can be taken independent of food, but should be taken with sufficient liquid. Lisinopril should only be taken once daily.

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

4.3 Contra-indications

- Hypersensitivity to lisinopril, excipients or other ACE-inhibitors.
- Prehistory of angioneurotic oedema in connection with treatment with an ACE-inhibitor, inherited or idiopatic angioneurotic oedema (see section 4.4).
- Hemodynamic relevant stenosis in aorta or mitral valves or hypertrophic cardiomyopathia.
- Systolic blood pressure $\leq$100 mmHg before start of treatment with lisinopril.
- Pregnancy or lactation (see section 4.6)
- Concomitant use of lisinopril and high-permeable membranes of poly(acrylnitril, sodium-2-methylallyl-sulphonate) (i.e. AN69) for crisis dialysis involves a risk of anaphylactic reactions (hypersensitivity reactions amounting to shock). This combination should therefore be avoided either by using other drugs than ACE-inhibitors for the treatment of hypertension and/or heart failure, or by using other membranes for dialysis (see section 4.4).
- Cardiogenic shock
- Severe renal impairment (creatinine clearance < 30 mL/min.)
- Hemodynamic unstable patients after acute myocardial infarction.

4.4 Special warnings and precautions for use

Treatment with lisinopril should be initiated in a hospital, in the case of patients receiving big or repeated doses of diuretics (> 80 mg furosemide), patients with hypovolemia, hyponatremia (serum sodium < 130 mmL/L), preexisting hypotension, unstable heartfailure, renal impairment, or patients on therapy with high doses of vasodilators as well as patients of the age of 70 years or older.

Hypotension

Lisinopril may cause a profound fall in the blood pressure, especially after the first dose. Symptomatic hypotension is rare in patients with uncomplicated hypertension. It is more likely to occur in patients, who are volume-depleted as a result of treatment with diuretics, dietary salt restriction, dialysis, diarrhoea or vomiting. It has been reported mainly in patients with severe heart failure, with or without concomitant renal insufficiency. This is more likely in patients on high doses of loop-diuretics, or in patients with hyponatremia or decreased renal function. In these patients the treatment should be initiated under close medical supervision, preferably in a hospital, with low doses, careful dose-titration, and concomitant control of the renal function and serum-potassium levels. If possible, the treatment with diuretics should be temporarily discontinued. Such conditions apply also to patients with ischemic heart- or cerebrovascular diseases in whom excessive hypotension may cause myocardial infarction or a cerebrovascular accident.

In case of hypotension the patient should be placed in supine position. Volume repletion with intravenous normal saline may be required. Atropine may be necessary in treatment of a herewith connected bradycardia. The appearance of hypotension after the initial dose, does not exclude a further careful dose-titration of the drug, after effective management.

If a non- acute hypotension in patients with heart diseases becomes symptomatic, a dose reduction and/or discontinuation of the treatment with diuretics and/or lisinopril may be necessary.

If possible, the treatment with diuretics should be discontinued for 2 to 3 days before the treatment with lisinopril is initiated.

Hypotension at acute myocardial infarction

The treatment with lisinopril must not be initiated in patients with acute myocardial infarction, if there exists a risk for further severe hemodynamic exacerbation after treatment with a vasodilator. This applies to patients with a systolic blood pressure of 100 mmHg or less or with cardiogenic shock. Maintenance dose should be reduced to 5 mg or temporarily to 2.5 mg, if the systolic blood pressure is 100 mmHg or less.

Treatment of patients with acute myocardial infarction with lisinopril may cause severe hypotension.

At persisting hypotension (systolic blood pressure of < 90 mmHg for more than 1 hour), lisinopril should be discontinued.

Patients with severely decreased heart function after acute heart attack, should only get lisinopril, if they are hemodynamic stable.

Renovascular hypertension /renal artery stenosis

There is an increased risk of severe hypotension and renal insufficiency, when patients with renovascular hypertension, and pre-existing bilateral renal artery stenosis or artery

stenosis in a single kidney are treated with lisinopril. Treatment with diuretics may be contributory cause to this. Loss of renal function may occur with only mild changes in serum creatinine, even in patients with unilateral renal artery stenosis. In these patients the treatment should be initiated in a hospital, closely supervised by a physician, with low doses and careful dose-titration. Treatment with diuretics should be discontinued, and the renal function should be monitored during the first week of therapy.

Renal insufficiency

Lisinopril is contra-indicated in patients with severely decreased renal function (creatinine clearance < 30 mL/min.) (see section 4.3). Lisinopril should be used with caution in patients with renal insufficiency, where lower or fewer doses may be necessary (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 in connection with lisinopril is mainly seen in patients with severe heart failure or with subjacent renal disease, inclusive renal artery stenosis. Renal failure in connection with lisinopril is normally reversible, if it is discovered immediately and is treated appropriately.

In some patients without apparent pre-existing renal disease, increases in blood-urea and serum creatinine have been observed, when a diuretic is given concomitantly. Dose reduction of lisinopril and/or discontinuation of the diuretic may be required.

At acute myocardial infarction the treatment with lisinopril should not be initiated in patients showing signs of decreased renal function, defined as serum creatinine concentration ≥177 micromol/L (2.0 mg/10 mL) and/or proteinuria over 500 mg/24h. If decreased renal function is developed during treatment with lisinopril (serum creatinine clearance < 30 mL/min or a doubling of the values before treatment), lisinopril should be discontinued.

There is no experience regarding the administration of lisinopril in renal transplant recipients. Treatment with lisinopril is therefore not recommended.

Hemodialysis

Concomitant use of lisinopril and high-permeable membranes of poly(acrylnitril, sodium-2-methylallyl-sulphonate) (i.e. AN69) during crisis dialysis or hemofiltration, are likely to experience anaphylactic reactions such as swelling of the face, flushing, hypotension and dyspnoea within few minutes after initiation of hemodialysis. It is recommended to use alternative membranes for dialysis or an alternative antihypertensive drug for treatment of hypertension or heart failure (see section 4.3).

Hyperpotassemia

Hyperpotassemia may occur during treatment with lisinopril, especially in the presence of renal insufficiency and/or heart failure. Potassium supplement 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 appropiate, they should be used with frequent monitoring of serum potassium.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism do generally not react on antihypertensive

drugs acting by inhibition of the renin-angiotensin-system. Use of lisinopril is therefor not recommended.

Proteinuria
It may occur, especially in patients with existing renal function impairment, or taking relatively large doses of lisinopril. Lisinopril should only be administered after critical evaluation of the risk/benefit of treatment of patients with clinical relevant proteinuria (more than 1g/day), and the clinical parameters as well as laboratory parameters should be regularly controlled.

Elderly
Some elderly patients may be more responsive to an ACE-inhibitor than younger patients. Administration of a low initial dose is recommended (2.5 mg lisinopril), and control of blood pressure, evaluation of renal function and/or representative laboratory parameters at the beginning of treatment is recommended.

LDL-lipidic apheresis/desensitization
The use of an ACE-inhibitor during LDL (low density lipoprotein) apheresis with dextrane sulphate may cause life-threatening anaphylactic reactions.

Life-threatening anaphylactic reactions (i.e. fall in blood pressure, dyspnoea, vomiting, allergic skin reactions) may also occur at concomitant administration of lisinopril and desensitization treatment of insect venom (i.e. bee- and wasp sting).

If LDL apheresis or desensitization treatment of insect venom is necessary , lisinopril should temporarily be replaced by other drugs (not ACE-inhibitors) for treatment of hypertension or heart failure.

Angioneurotic oedema (see section 4.3)
Angioneurotic oedema of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients on treatment with ACE-inhibitors, incl. lisinopril which especially occurs during the first weeks of treatment. However, in rare cases severe angioedema may develop after long-term treatment with an ACE-inhibitor. In such cases lisinopril should be discontinued immediately, and replaced by an agent belonging to another class of products.

In the cases where the swelling is limited to face and lips, the condition normally ceases without treatment, however, antihistamines may be tried for alleviation of the symptoms.

Patients, who earlier have suffered from angioneurotic oedema without connection with ACE-inhibitor treatment, may have an increased risk of development of angioneurotic oedema after intake of an ACE-inhibitor. Angioneurotic oedema, where tongue, glottis and/or larynx are involved, may be fatal. Emergency therapy should be initiated, including, but not necessarily limited to, immediate subcutaneous injection of 0.3 to 0.5 mg adrenaline epinephrine solution 1:1000 or slow intravenous administration of adrenaline 1 mg/ml (please watch clog ups and dilution instructions), with control of ECG and blood pressure. Hospitalization of patients is necessary. Appropriate control should be initiated over minimum 12 to 24 hours to ensure, that the symptoms are completely disappeared, before the patient is discharged.

ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients.

Aorta stenosis/myocardial hypertrophy
ACE-inhibitors should be used with caution in patients with an obstruction in the outflow tract of the left ventricle. Lisinopril is contra-indicated, if the hypertrophy is hemodynamic relevant.

Neutropenia/agranulocytosis
The risk of neutropenia appears to be dose-and type- related and is dependent on patient's clinical status. It is rarely seen in patients with uncomplicated hypertension, but may occur in patients with some degree of renal impairment, especially if it is associated with collagen vascular disease (i.e. systemic lupus erythematosus or sclerodermia) and therapy with immunosuppressive agents. The white blood cells of these patients should be controlled regularly. It is reversible after discontinuation of the ACE inhibitor.

Cough
Cough has been reported during treatment with ACE-inhibitors. The cough is usually dry and non-productive and disappears after discontinuation of treatment.

Surgery/anaesthesia
Lisinopril may cause hypotension or even hypotensive shock in patients undergoing major surgery or during anesthesia through the enhancement of other hypotensive potentials. This hypotension may be corrected by volume expansion (see section 4.5).Treatment with lisinopril should be discontinued the previous day before the operation.

4.5 Interaction with other medicinal products and other forms of interaction

Diuretics
When a diuretic is administered together with lisinopril, the antihypertensive effect is usually additive. Patients on diuretics and especially those who are volume- and/or salt depleted, may experience an excessive reduction in blood pressure, after initiation of therapy with lisinopril. The possibility of symptomatic hypotension during treatment with lisinopril can be minimised by discontinuation of diuretics before start of lisinopril treatment (see sections 4.2 and 4.4)., by increasing volume or salt intake prior to intake and by initiation of therapy with lower doses of the ACE-inhibitor. Further increases in dosage should be made with caution.

Potassium-sparing diuretics and potassium supplement
Potassium-sparing diuretics may give an additive potassium increasing effect, especially at decreased renal function. ACE-inhibitors attenuate a diuretic induced loss of potassium. Administration of potassium-sparing diuretics (as i.e. spironolactone, triamterene or amiloride), potassium supplement or potassium containing salt substitutes, may cause a significant increase in serum potassium. If concomitant use is indicated because of demonstrated hypopotassemia, they should be used with caution and with frequent monitoring of serum potassium.

Sodium chloride
Reduces fall in blood pressure and effect on symptoms of heart failure, and weakens hereby the effect of lisinopril.

Antihypertensive agents
Increase of the hypotensive effect of lisinopril

Analgesics and anti-inflammatoriy agents (i.e. acetyl salicylic acid, indomethacin)
May reduce the antihypertensive effect of lisinopril.

Lithium
The concomitant administration of ACE inhibitors with lithium may reduce the lithium excretion. The serum-lithium-levels should therefore be strictly monitored, if lithium salts are going to be used. The posology should be adapted when necessary.

Alcohol
ACE-inhibitors increase the effect of alcohol. Alcohol fortifies the antihypertensive effect of ACE-inhibitors.

Anaesthetics/narcotics/hypnotics
ACE inhibitors may enhance the hypotensive effect of certain anaesthetic medicinal products (the anaesthesiologist should be informed about the lisinopril treatment.)

Sympatomimetics
May reduce the antihypertensive effect of ACE-inhibitors.Patients should be carefully monitored to confirm that the desired effect is being obtained.

The risk of leucopenia is increased in concomitant treatment with allopurinol, cytostatics or immunosuppressive agents, systemic corticoides or procainamide.

Oral antidiabetics (i.e. sulfonyl urea/biguanides), insulin
ACE-inhibitors may fortify the hypoglycaemic effect of antidiabetics, especially during the first weeks of combination treatment.

Antacids
Induce decreased bioavailability of ACE inhibitors.

Non-steroidal 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 in serum potassium, whereas renal function may decrease. These effects are in principle reversible, and occur especially in patients with compromised renal function.

4.6 Pregnancy and lactation

Pregnancy: lisinopril is contra-indicated during pregnancy (see section 4.3).

No appropriate and well controlled studies have been performed in humans. ACE-inhibitors pass placenta and may cause foetal and neonatal disease and death, when administered to pregnant women.

If embryos are exposed to ACE-inhibitors during second or third trimester, it may cause neonatal hypotension, renal failure, deformities of face or cranium and/or death. Oligohydramnios in the mother has been reported, reflecting decreased foetal renal function. Shortening of the limbs, deformities of the cranium, development of hypoplastic lungs and intrauterine growth-inhibition, have also been connected with oligohydramnios.

New born, who have been exposed to ACE-inhibitors as embryos, should be observed closely with respect to hypotension, oliguira and hyperpotassemia. At oliguira a treatment of blood pressure and renal perfusion should be performed.

Intrauterine growth-inhibition, premature birth, open ductus arteriosus and foetal death have been reported, but it is unclear, if this causes ACE-inhibition or subjacent disease

of the mother.

It is not known, if the foetus is unfavourably influenced, if the exposure to ACE-inhibitors is limited to the first trimester. Women, who get pregnant during treatment with an ACE-inhibitor, should be informed about the possible risk for the foetus.

Lactation: ACE inhibitors are excreted in breast milk. The effect on the breast fed child has not been investigated. Breast feeding is not recommended, when the mother is treated with an ACE inhibitor.

4.7 Effects on ability to drive and use machines

There are no studies of the effect on the ability to drive a car. At car driving or handling of machines, it should be taken into consideration, that dizziness and fatigue may occur.

4.8 Undesirable effects

The following undesirable effects have been observed during treatment with lisinopril and other ACE-inhibitors:

Cardiovascular system
Occasionally hypotension at the beginning of treatment or at increase of the dose of lisinopril and/or diuretic may occur. This is especially observed in high-risk patients, i.e. patients who are salt- or volume depleted after diuretic treatment, heart failure, and severe or renal hypertension. Symptoms as dizziness, sense of fatigue, disturbed vision, rarely accompanied by unconsciousness (syncope) may occur.

Individual cases of tachycardia, palpitations, arrhytmias, chest pain, angina pectoris, myocardial infarction, transient ischemic attacks and strokes have been reported for ACE-inhibitors in connection with profound fall in blood pressure.

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

Kidneys
Renal insufficiency may occur or be intensified. Single cases of acute renal failure have been reported. Proteinuria, partly with simultaneous reduction of the renal function has been observed.

Respiratory system
Occasionally dry cough, sore throat, hoarseness and bronchitis, rarely dyspnoea, sinusitis, rhinitis, bronchospasms/asthma, lung infiltration, stomatitis, glossitis and dry mouth may occur.

In individual cases, fatal blocking of the upper part of the respiratory tract because of angioneurotic oedema in has occurred (see section 4.4).

Isolated cases of allergic alveolitis (eosinophilic pneumonia) are related to lisinopril treatment.

Gastro-intestinal tract/liver
Occasionally nausea, abdominal pain and indigestion, rarely vomiting, diarrhoea, constipation and loss of appetite may occur.

ACE-inhibitors may in rare cases cause a syndrome of jaundice, suddenly severe hepatic necrosis and death. The mechanism of this syndrome is not known. If jaundice

develops during treatment with ACE-inhibitors, the treatment should be discontinued and the patient should be examined by a physician

Individual cases of hepatic failure, hepatitis, decreased liver function, pancreatitis and ileus have been described.

Skin, vessels
Occasionally allergic skin reactions as rash, rarely pruritus, urticaria and angioneurotic oedema in face, lips and/or limbs may occur.

Isolated cases of severe skin reactions include pemphigus, erythema, exfoliative dermatitis, Steven-Johnson's syndrome and toxic epidermal necrolysis.

Skin reactions may be accompanied by fever, myalgia, arthralgia, vasculitis, eosinophilia, leucocytosis and/or positive ANA. If severe skin reaction is suspected, the responsible physician should be consulted immediately, and the treatment with lisinopril should be discontinued.

Individual cases of psoriasis like skin changes, photosensitivity, blushing, sweat tendency, alopecia, onycholysis and aggravation of Raynaud's disease are described.

Nervous system
Occasionally head ache and fatigue. Rarely somnolence, depressions, sleep disturbances, impotence, peripheral neurophatia with paresthesia, disturbances in the sense of equilibrium, muscle convulsions, nervousness, confusion, tinnitus, blurred vision, taste disturbances and temporarily loss of taste.

Laboratory parameters (blood, urine)
Occasionally a reduction in hemoblobin, hematocrit, number of white blood cells and platelets may occur. Rarely anaemia, thrombocytopenia, neutropenia and eosinophilia occur.

Isolated cases of agranulocytosis and pancytopenia, especially in patients with decreased renal function, collagen disease or in concomitant treatment with allopurinol, procainamide or certain immunosuppressive drugs, have been observed.

Cases of hemolytic anaemia in patients with congenital loss of the enzyme glucose-6-phosphate-dehydrogenase (G6-PD) are reported.

In patients with renal insufficiency, severe heart failure and renovascular hypertension, an increase in serum-creatinine, serum-urea and serum-potassium or fall in concentration of serum-sodium, may rarely occur. In diabetic patients hyperpotassemia has been observed.

Proteinuria may increase in special cases (se section 4.4).

Isolated cases of increase of liver enzymes and serum-bilirubin have been observed.

Special remarks
The above mentioned laboratory parameters should be controlled before treatment with lisinopril and regularly during treatment. Measuring of serum-electrolytes and serum-creatinine as well as full blood count should be performed, especially in the first phase of treatment and in high risk patients (patients with renal insufficiency with collagen disease), and in concomitant treatment with immunosupressiva or cytostatics, allopurinol and procainamide.

If patients on treatment with lisinopril show symptoms of fever, swelled lymph glands and/or sore throat, a control of the white blood cells should be performed as quick as possible.

4.9 Overdose

No data concerning overdose in humans are available. The most likely phenomena in overdosing would be hypotension, where the usual treatment would be infusion of standard saline solution. Lisinopril may be removed from blood by hemodialysis.

After intake of an overdose the patient should be closely supervised, preferably in the intensive care unit in a hospital. Serum-electrolytes and serum-creatinine should be controlled regularly. Precautions should be taken against absorption, as gastric emptying, administration of adsorbents and sodium sulphate within 30 minutes after intake of the overdose and accelerated elimination, if the overdose has be taken recently.

If hypotension occurs, the patient should be placed in shock position, and intravenous salt and volume supplement should be given quickly. Treatment with angiotensin II should be considered. Bradycardia should be treated with atropine. Use of pace-maker may be considered. ACE-inhibitors may be removed from circulation by hemodialysis. Use of high permeable polyacrylnitril-membranes should be avoided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: C09A A03
Lisinopril inhibits the angiotensin converting enzyme (ACE). The angiotensin converting enzyme is a peptidyl-dipeptidase, catalysing the conversion of angiotensin I to the vasocontracting peptide, angiotensin II. Inhibition of ACE results in decreased plasma-angiotensin II concentration, resulting in an increased plasma renin activity (because of removal of the negative feedback from the renin release) and a reduced aldosterone secretion.

ACE is identical with kininase-II. Therefor lisinopril may also block the decomposition of bradykinin, which is a potential vasodepressive peptide. To which extent this has an importance for the therapeutic effect of lisinopril has not yet been elucidated.

Although the mechanism, by means of which lisinopril decreases the blood pressure, is anticipated to be primarily a suppression of the renin-angiotensin-aldosterone system, it is shown, that lisinopril also has an antihypertensive effect in patients with low-renin hypertension.

5.2 Pharmacokinetic properties

Measurements of urine excretion in clinical trials have shown that the average absorption fraction is approximately 29% (22-50%), with an inter-patient variation of 6-60% at all doses tested (5-80mg). The maximum plasma concentration was achieved within approximately 7 hours after oral administration. The absorption of lisinopril is not affected by the presence of food in the gastro-intestinal tract.

Lisinopril is not metabolised and the absorbed moiety is excreted completely and unchanged in the urine. Following multiple doses, 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. This 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.

Acute myocardial infarction patients, however, tended towards a slightly longer time to peak plasma concentration. Impaired renal function reduces the excretion of lisinopril through the kidneys. Dosage adjustment is recommended to patients with creatinine clearance < 70 ml/min (see 4.2).

5.3 Preclinical safety data

In animal studies lisinopril has been found to have effects related to its pharmacological class, large doses cause renal tubular degeneration. No teratogenic effect has been found. Fetotoxicity can be induced in mice and rabbits related to the pharmacological effects of the drug. Lisinopril has not been shown to have a mutagenic effect and carcinogenicity studies have not revealed untoward effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, calcium hydrogen phosphate dihydrate, pregelatinised maize starch, croscarmellose sodium, magnesium stearate, Pigment Blend PB-24823 (pregelatinised maize starch, iron oxide red, iron oxide black and iron oxide yellow (E 172) (only 10 mg Lisinopril “Biochemie” tablets) and Pigment Blend PB 24824 (pregelatinised maize starch, iron oxide red, iron oxide black and iron oxide yellow (E 172) (only 20 mg Lisinopril “Biochemie” tablets).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

5 mg: Do not store above 25ºC
10 mg and 20 mg: No special precautions for storage

6.5 Nature and contents of container

PVC/aluminium blisters and/or PP-securitainers with a dessicant
Packsizes:
5 mg tablets: 14, 28, 30, 56, 60, 98, 100, 100 x 1, 250, 500 tablets
10 mg tablets: 28, 30, 100, 100 x 1, 250 tablets
20 mg tablets: 14, 28, 30, 56, 98, 100, 100 x 1, 250, 500 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

<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.>