Safeguarding public health

MHRA

Public Assessment Report

RAMIPRIL 1.25 MG TABLETS
RAMIPRIL 2.5 MG TABLETS
RAMIPRIL 5 MG TABLETS
RAMIPRIL 10 MG TABLETS

(RAMIPRIL)

PL 18843/0014-17

Medicines and Healthcare products Regulatory Agency

RAMIPRIL TABLETS

(RAMIPRIL) PL 18843/0014-17

UKPAR

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RAMIPRIL 1.25, 2.5, 5 AND 10MG TABLETS (RAMIPRIL)
PL 18843/0014-17

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Endwell Limited a Marketing Authorisation (licence) for the medicinal product Ramipril 1.25, 2.5, 5 and 10 mg Tablets (PL 18843/0014-17). Ramipril is an angiotensin converting enzyme (ACE) inhibitor indicated for treatment of mild to moderate hypertension, adjunctive therapy for congestive cardiac failure and for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation in defined patient groups. This is a prescription only medicine [POM].

Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active angiotensin converting enzyme (ACE) inhibitor, ramiprilat. Administration of ramipril causes an increase in plasma renin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance.

The clinical data presented to the MHRA, before licensing, demonstrated that ramipril tablets is bioequivalent to the reference product, Delix Tablets, first approved in Germany 16th August 1993 (Hoescht MR, Germany) and Ramipril tablets are marketed in the UK by Aventis Pharma Limited, under the brand name 'Tritace' (PL 04425/0356-0359). Marketing authorisations were approved for these products in the UK on 30 September 2003.
Based on the information provided, ramipril tablets from Endwell are interchangeable with 'Tritace' tablets.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using ramipril tablets outweigh the risks, hence a Marketing Authorisation has been granted.

RAMIPRIL 1.25, 2.5, 5 AND 10MG TABLETS

(RAMIPRIL)

PL 08553/0212

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products ramipril tablets (PL 18843/0014-17) to Endwell Limited on 5th April 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1 [formerly Article 10.1(a)(iii)] of Directive 2001/83/EC as amended, claiming essential similarity to Delix Tablets (Hoescht MR) first approved in Germany on 16th August 1993.

The product contains the active ingredient ramipril. Ramipril is an angiotensin converting enzyme (ACE) inhibitor indicated for treatment of mild to moderate hypertension, adjunctive therapy for congestive cardiac failure and for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation in defined patient groups.

Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active ACE inhibitor, ramiprilat. Administration of ramipril causes an increase in plasma renin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 18843/0014-17
PROPRIETARY NAME: Ramipril 1.25, 2.5, 5 and 10mg Tablets
ACTIVE(S): Ramipril
COMPANY NAME: Endwell Limited
E.C. ARTICLE: Article 10.1 [formerly Article 10.1(a)(iii) of Directive 2001/83/EC]
LEGAL STATUS: POM

1. INTRODUCTION

1.1 Legal Basis

These are national, abridged applications submitted under article 10.1 and claiming essential similarity to Delix Tablets (1.25mg-10mg), marketed by Hoescht MR in Germany. The date of first approval in Germany is stated as 16th August 1993. Ramipril tablets are marketed in the UK by Aventis Pharma Limited, under the brand name 'Tritace' (PL 04425/0356-0359). Marketing authorisations were approved for these products in the UK on 30 September 2003.

1.2 Use

Ramipril is an angiotensin converting enzyme inhibitor indicated for treatment of mild to moderate hypertension, adjunctive therapy for congestive cardiac failure and for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation in defined patient groups. Dosage is dependent on the condition and response in the range 1.25 to 10mg daily.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Ramipril 1.25, 2.5, 5 and 10mg Tablet. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The products contain Ramipril equivalent to 1.25, 2.5, 5 and 10mg of Ramipril respectively. The tablets are packed into aluminium/aluminium blisters or polypropylene continers with polyethylene closures and containing a desiccant. The proposed shelf-life (18 months) and storage conditions (Do not store above 25°C) are consistent with the details registered for the cross-reference products.

2.3 Legal status

These products will be subject to a medical prescription.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is Endwell Limited, Elm House, Ashbourne Industrial Estate, Ashbourne, Co. Meath, Ireland.

The Qualified Person responsible for pharmacovigilance is stated and their CV is included.

2.5 TSE

The applicant has provided a declaration that the only material of animal origin used in manufacture of the finished product is lactose (tablet excipient and constituent of pigment blend). Statement have been provided from lactose suppliers (DMV International and Borculo Domo) that the milk used in manufacture of lactose is sourced from healthy animals under the same conditions as that for human consumption. Calf rennet used in production of raw material whey (DMV) is in accordance with EMEA/CPMP/571/02. This is acceptable.

DRUG SUBSTANCE

Two sources of active substance are approved. The active substances from these sources are the subject of Drug Master Files (DMF). Full assessment of the DMFs has been performed.

A copy of the current DMFs edition of the applicant's part has been provided in the CTD format. Letters of access are provided**.**

Satisfactory drug substance specifications are included in the DMFs.

The finished product manufacturer has also provided a drug substance specification. Certificates of Analysis (CoAs) for batches of the drug substance tested on receipt have been provided.

Analytical Procedures

Analytical procedures are described.

Validation of Analytical Procedures

Satisfactory validation data are provided for the analytical procedures.

Batch Analysis

Results of industrial scale batches of ramipril are within specification.

Reference standards

Satisfactory primary and working reference standards are identified.

Stability

Batches stored under ICH real time conditions show compliance with set limits during the approved retest period.

DOSAGE FORM

Composition

The composition is satisfactory and tabulated below.

Name of constituents	Function	Reference to Standards
Active constitutent		
Ramipril	Active	Ph. Eur
Other constitutents		
Sodium hydrogen carbonate	Stabiliser	Ph. Eur
Lactose monohydrate	Filler	Ph. Eur
Croscarmellose sodium	Disintegrant	Ph. Eur
Pregelatinized starch (Starch 1500)	Filler/ disintegrant	Ph. Eur
Sodium stearyl fumarate	Lubricant	Ph. Eur
Pigment Blend PB 22960 Yellow Lactose monohydrate Iron oxide yellow	Colouring agent	 Ph. Eur NF
Pigment blend PB24877 Pink Lactose monohydrate Iron oxide red Iron oxide yellow	Colouring agent	 Ph. Eur NF NF
Tablet weight (mg)		

PHARMACEUTICAL DEVELOPMENT

Drug Substance

Ramipril is slightly soluble in water and freely soluble in methanol. It does not show polymorphism.

Excipients

The excipients chosen for the ramipril tablets are the same as in the commercially available Delix Tablets (Hoescht MR, Germany). The formulation is film-coated tablets, comprising of excipients that comply with Ph. Eur except the iron oxide red and yellow that complies with the United States National Formulary (NF). The function and concentration of the excipients used is standard and accepted.

Pharmacokinetic studies

Satisfactory CoAs are provided for the biobatches.

Container Closure System

The tablets are packed into aluminium/aluminium blisters or polypropylene containers with polyethylene closures and containing a desiccant. Pack sizes of 7, 14, 21, 28, 30, 50 and 100 tablets are approved for marketing.

Data are provided for the primary packaging to show compliance with EU food safety requirements

Microbiological Attributes

The microbiological attributes are controlled in the finished product specification to Ph. Eur. 5.1.4 category 3A and accepted.

Compatibility

Stated 'not relevant' but can be inferred from the product stability data, and accepted.

MANUFACTURE

GMP Statement and Manufacturing Chain

The site of batch release is Actavis Limited, Reykjavikurvegur 78, Hafnarfjordur, IS-220, Iceland. The sites of manufacture and assembly are also stated. A satisfactory copy of the GMP certificate issued by the Icelandic Medicines Agency has been provided. In accordance with GMP arrangements within the EEA, this is acceptable.

Description of the Manufacturing Process

A satisfactory formula and description of manufacture are provided.
There are no re-processing data provided.

Critical phases of the manufacturing process have been satisfactorily identified and appropriate in-process controls are in place.

The analytical methods and limits are the same as those used in finished product testing and comply with current guidelines and accepted. The tablets are blister packed with satisfactory in-process controls.

In-process batch data for validation batches are satisfactory. The validation results demonstrate homogeneity of blends and consistent manufacture.

The validation protocol provided is considered adequate for the purpose.

Control of Excipients

The list of excipients, complying with Ph. Eur. requirements, is given under "Composition of the medicinal product" above. Iron oxide red and yellow comply with the National Formulary (NF).

Satisfactory Certificates of Analysis have been provided for each excipient and are accepted. The compendial methodology is used in testing.

Specifications
A satisfactory finished product specification is provided.

Analytical Procedures
Satisfactory validation data are provided.

Batch data
Satisfactory data are provided for batches manufactured at the proposed site and are considered representative of the product to be marketed. Dissolution data including standard deviations and profiles are reported.

Characterisation of Impurities
This is satisfactory.

Reference Samples
Reference samples are identified.

Container Closure System
Satisfactory details of supplier specification, product construction, standards and compliance statements are provided. In-house specification giving details of tests performed on receipt are provided.

Standard Storage Conditions
Based on stability data at normal, intermediate and accelerated conditions. The data support the a product shelf-life of 18 months and the storage direction 'do not store above 25°C, store in the original package' is approved.

The samples provided for stability studies are representative of the product to be marketed in the proposed pack.

The programme is ongoing. The stability programme is satisfactory as the applicant has agreed to place the first commercial batches on stability.

The results of the stability studies support the proposed shelf life.

Bioanalytical Methods and Validation
Satisfactory methodology and validation data are provided.

Quality Overall Summary
This is satisfactory.

Essential Similarity
The following data support essential similarity:

a) Acceptable choice of test and reference products
b) Acceptable bioequivalence between test and reference product.
c) Comparative dissolution profiles are provided for test and reference product.
d) The impurity profile of the test product is comparable with that of the reference product and considered satisfactory.

e) The active substances conform to Ph. Eur. requirements and comply with relevant principles in ICH guidelines.

PRODUCT PARTICULARS

Product Brand Name
This is considered satisfactory.

Summary of Product Characteristics
Satisfactory SPC provided.

Patient Information Leaflet
Satisfactory coloured mock-ups are provided**.** The applicant has until 1st July 2008 to amend the order in which the information appears in the leaflet and provide user testing data (both parts of Article 59, Directive 2004/27/EC must be complied with at the same time).

Labelling
Satisfactory.

MARKETING AUTHORISATION APPLICATION (MAA) form
This is satisfactory.

ADDITIONAL DATA REQUIREMENTS
Satisfactory.

CONCLUSION
A product licence may be granted for this product.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND

This is a generic application for ramipril tablets. The original product referred to is Delix tablets (Hoechst M.R) authorised in Germany on 16 August 1993. Essential similarity is claimed with Tritace (Aventis Pharma ,PL: 04425/0356).

ACE inhibitors exhibit their pharmacological effects by inhibiting the formation of Angiotensin II, which has strong vasoconstrictive effect. They have been used as antihypertensive and when given early, also to reduce mortality and cardiovascular morbidity in patients with myocardial infarction.
Ramipril is a long acting ACE inhibitor, is a prodrug and forms active metabolite ramiprilat. The safety and efficacy of ramipril in various indications has been established.

2. INDICATIONS

For reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Also for reducing the risk of myocardial infarction cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have one or more of the following clinical findings:

- hypertension (systolic blood pressure >160mmHg or diastolic blood pressure >90mmHg);
- high total cholesterol >5.2mmol/L);
- low HDL (<0.9mmol/L);
- current smoker;
- known microalbuminuria;
- clinical evidence of previous vascular disease.

Ramipril Tablets are indicated for the treatment of mild to moderate hypertension.

Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

Ramipril Tablets have been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure."

3. DOSE & DOSE SCHEDULE

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures: The recommended initial does is 2.5mg Ramipril once a day. Depending on the tolerability, the dose should be gradually increased. Therefore, it is recommended that this dose is doubled after about one week of treatment

then, after a further 3 weeks, it should be finally increased to 10mg. The usual maintenance dose is 10mg Ramipril once a day. Patients already stabilised on lower doses of Ramipril for other indications where possible should be titrated to 10mg Ramipril once daily.

Hypertension: The recommended initial dosage in patients not on diuretics and without congestive heart failure is 1.25mg Ramipril once a day. Dosage should be increased incrementally at intervals of 1-2 weeks, based on patient response, up to a maximum of 10mg once a day.

A 1.25mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5-5mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10mg Ramipril, combination treatment is recommended.

In diuretic treated patients, the diuretic should be discontinued 2-3 days before beginning therapy with Ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required.

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25mg under close medical supervision in hospital.

Congestive heart failure: Recommended initial dose: In patients stabilised on diuretic therapy the initial dose is 1.25mg once daily. Depending on the patient's response, the dose may be doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5mg or more is required, this may be taken as a single dose or as two divided doses. Maximum permitted daily dose: 10mg.

In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting Ramipril treatment.

Post myocardial infarction: Treatment must be started in hospital between day 3 and day 10 following acute myocardial infarction. The starting dose is 2.5mg twice a day, which is increased to 5mg twice a day after 2 days. If the initial 2.5mg dose is not tolerated a dose of 1.25mg twice a day should be given for two days before increasing to 2.5mg and 5.0 mg twice a day. If the dose cannot be increased to 2.5mg twice a day treatment should be withdrawn. The maintenance dose is 2.5 to 5mg twice a day.

Dosage adjustment in renal impairment: The usual dose of Ramipril is recommended for patients with a creatinine clearance>30ml/min (serum creatinine <165μmol/l). For patients with a creatinine clearance <30ml/min (serum creatinine >165μmol/l) the initial dose is 1.25mg Ramipril once a day and the maximum dose 5 mg Ramipril once a day.

In patients with severe renal impairment (creatinine clearance <10ml/min and serum creatinine of 400-650μmol/l), the recommended initial dose is also 1.25mg Ramipril once a day, but the maintenance dose should not exceed 2.5mg Ramipril once a day.

Dose in hepatic impairment: In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in

elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25mg under close medical supervision in patients with impaired liver function.

Elderly: Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

Children: Ramipril has not been studied in children, and therefore use in this age group is not recommended.

Ramipril tablets should be taken with a glass of water. The absorption of ramipril is not affected by food".

4. TOXICOLOGY

Not assessed.

5. CLINICAL PHARMACOLOGY

Ramirpril is a prodrug, which is hydrolysed in the liver to form the active angiotensin converting enzyme inhibitor ramiprilat.
The kinetic profile of ramipril is known as it has already been authorised and in clinical use for many years. The applicant has investigated the bioequivalence of the product compared with the reference product (Delix, Hoechst AG 2.5mg tablets authorised in Germany in 1993 and Tritace 10mg tablets, Aventis Pharma Ltd).

5.1 BIOEQUIVALENCE

The applicant has provided data from two bioequivalent studies. The first one compared two tablets of 2.5mg strength and the other one compared 10mg tablets with the reference product.
The bioequivalence of Delta ramipril 5 mg (2×2.5mg tablets) was compared with Delix (Hoechst AG) 2.5mg tablets in a randomised, open-label, single-dose, 2-way, cross-over study. A total of 36 healthy volunteers were recruited in the study and 35 analysed. The clinical expert report suggests 38 volunteers entered the study but statistical analysis were performed on 35 subjects.
The washout period was 28 days and products were administered under fasting conditions.

The results and kinetic profile for the parent compound as well as active metabolite is shown in the table below.

Ramipril 5mg (2×2.5mg tablets)

	Least squires mean	Least squares mean	Ratio of least squares means	90% CI
	Test (Delta)	Reference Delix(Hoechst AG)		
In AUC $_{0-4}$ (ng.h/ml)	8.84	8.89	99.2%	94.3 – 104.4
In AUC $_{0-inf}$ (ng.h./ml)	9.45	9.25	102.4	96.6 – 108.4
Ln Cmax (ng/ml)	11.32	12.43	90.8	81.3 - 101
Tmax (h)	0.576	0.456		

Ramiprilat

	Least squares mean	Least square mean	Ratio of least square means	90% CI
	Test (Delta)	Reference Delix (Hoechst AG)		
In AUC $_{0-4}$ (ng.h/ml)	150.3	150.71	100%	97.3 – 102.8%
In AUC $_{0-inf}$ (ng.h/ml)	226.11	223.87	101.3%	96.9 – 105.8%
Ln Cmax (ng/ml)	7.62	7.49	102.3%	95.5 – 109.6%
Tmax (h)	2.85	3.02		

The second study was similar in design. Patients either received ramipril10mg tablet (Delta Ltd) or ramipril 10mg tablet (Aventis Pharma, Delix). A total of 36 subjects were planned and analysed (study report). The results were as follows:

Ramipril 10mg tablets

	Least squires mean	Least squares mean	Ratio of least squares means	90% CI
	Test (Delta)	Reference Delix(Hoechst AG)		
In AUC $_{0-4}$ (ng.h/ml)	17.95	16.93	106%	98.0 – 114.6%
In AUC $_{0-inf}$ (ng.h./ml)	18.73	17.64	106.1%	98.6 – 114.5%
Ln Cmax (ng/ml)	21.79	20.54	106%	93.8 – 119.8%
Tmax (h)	0.69	0.53		

Ramiprilat

	Least squares mean Test (Delta)	Least square mean Reference Delix (Hoechst AG)	Ratio of least square means	90% CI
In AUC $_{0-4}$ (ng.h/ml)	228.36	220.69	103.5%	100.8 – 106.2%
In AUC $_{0-inf}$ (ng.h/ml)	314.68	299.03	105.2%	102 – 108.6%
Ln Cmax (ng/ml)	20.04	18.91	106%	99.4 – 112.9%
Tmax (h)	2.472	2.486		

Assessor's comments*: The first bioequivalence study was conducted with 2.5mg tablets (2 tablets given to make up 5mg dose). The PK parameters show bioequivalence. The reference products were acceptable. The second study with 10mg tablets also show bioequivalence of the 10mg ramipril test tablets.*

6. EFFICACY

Efficacy of ramipril is known through its clinical use over many years and extensive publications. The clinical expert report has addressed the various indications for this product. No new data has been submitted and none is required.

7. SAFETY

The clinical safety of the product is well established. No new data has been submitted and none is required.

8. EXPERT REPORT

A Clinical Overview has been provided in CTD Module 2.5.
A Clinical Summary has not been provided in CTD Module 2.7.
Information about the Clinical Expert is provided in CTD Module 1.4.3.

9. SUMMARY OF PRODUCT CHARACTERISTICS

The SPCs are considered satisfactory and are consistent with the PILs for the reference product.

10. PATIENT INFORMATION LEAFLET

The PILs are considered satisfactory and are consistent with the PILs for the reference product.

11. LABELLING

The labelling is considered satisfactory.

13. DISCUSSION

The clinical use of ramipril is well established in the indications proposed. The bioequivalence of the tablets have been shown. No new clinical efficacy and safety data has been submitted and none is required.

12. CONCLUSIONS

Overall, there is no clinical objection to the grant of marketing authorisations for these applications. No new or unexpected safety concerns arise from these applications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for these applications are consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Ramipril is a well known drug and has been used as an ACE inhibitor for many years. Bioequivalence has been demonstrated between the applicant's ramipril tablets and the innovator product, Delix Tablets. No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with ramipril is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

RAMIPRIL 1.25, 2.5, 5 AND 10MG TABLETS (RAMIPRIL)
PL 08553/0212

RAMIPRIL 250MG TABLETS (RAMIPRIL)
PL 08553/0213

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 20th May 2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 10th November 2005.
3	Following assessment of the application the MHRA requested further information on 15th March 2006.
4	The applicant responded to the MHRA's requests, providing further information on 29th March 2006.
7	The application was determined on 5th April 2006.

RAMIPRIL 1.25, 2.5, 5 AND 10MG TABLETS

(RAMIPRIL)

PL 18843/0014-17

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

RAMIPRIL 1.25 MG TABLETS (RAMIPRIL)
PL 18843/0014

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 1.25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ramipril, 1.25 mg

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
White, capsule shaped, uncoated, flat tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Also for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings:

- hypertension (systolic blood pressure > 160mmHg or diastolic blood pressure > 90mmHg);
- high total cholesterol (>5.2 mmol/L);
- low HDL (<0.9 mmol/L);
- current smoker;
- known microalbuminuria;
- clinical evidence of previous vascular disease.

Ramipril Tablets are indicated for the treatment of mild to moderate hypertension.

Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

Ramipril Tablets have been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure.

4.2 Posology and method of administration

Oral administration.

Dosage and Administration:

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures: The recommended initial dose is 2.5 mg Ramipril once a day. Depending on the tolerability, the dose should be gradually increased. Therefore, it is recommended that this dose is doubled after about one week of treatment then, after a further 3 weeks, it should be finally increased to 10 mg. The usual maintenance dose is 10 mg Ramipril once a day. Patients

already stabilised on lower doses of Ramipril for other indications where possible should be titrated to 10 mg Ramipril once a day.

***Hypertension*:** The recommended initial dose in patients not on diuretics and without congestive heart failure is 1.25 mg Ramipril once a day. Dosage should be increased incrementally at intervals of 1 - 2 weeks, based on patient response, up to a maximum of 10 mg once a day.

A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5 -5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg Ramipril, combination treatment is recommended.

In diuretic treated patients, the diuretic should be discontinued 2 - 3 days before beginning therapy with Ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required.

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25 mg under close medical supervision in hospital.

***Congestive heart failure*:** The recommended initial dose in patients stabilised on diuretic therapy the initial dose is 1.25 mg once a day. Depending on the patient's response, the dose may be increased. If the dose is increased it is recommended that it is doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. The maximum permitted daily dose is 10 mg.

In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting Ramipril treatment.

Post myocardial infarction: Treatment must be started in hospital between day 3 and day 10 following acute myocardial infarction. The starting dose is 2.5 mg twice a day which is increased to 5 mg twice a day after 2 days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5.0 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day, treatment should be withdrawn.
The maintenance dose is 2.5 to 5.0 mg twice a day.

***Dosage adjustment in renal impairment*:** The usual dose of Ramipril is recommended for patients with a creatinine clearance > 30 ml/min (serum creatinine < 165 μmol/l). For patients with a creatinine clearance < 30 ml/min (serum creatinine >165 μmol/l) the initial dose is 1.25 mg Ramipril once a day and the maximum dose 5 mg Ramipril once a day.

In patients with severe renal impairment (creatinine clearance < 10 ml/min and serum creatinine of 400-650 μmol/l), the recommended initial dose is also 1.25 mg Ramipril once a day, but the maintenance dose should not exceed 2.5 mg Ramipril once a day.

***Dosage in hepatic impairment*:** In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg under close medical supervision in patients with impaired liver function.

***Elderly*:** Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

***Children*:** Ramipril has not been studied in children, and therefore use in this age group is not recommended.

Ramipril tablets should be taken with a glass of water. The absorption of ramipril is not affected by food.

4.3 Contraindications

Hypersensitivity to ramipril or any of the excipients. History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients. Pregnancy. Lactation.

4.4 Special warnings and precautions for use

***Warnings*:**

Ramipril should not be used in patients with aortic or mitral valve stenosis or outflow obstruction.

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

***Precautions*:**

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

Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of Ramipril; their renal function should be closely monitored. In the majority, renal function will not alter. There is a risk of impairment of renal function, particularly in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal artery stenosis in the single kidney as well as after renal transplantation. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

Patients haemodialysed using high flux polyacrylonitrile ('AN69') membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for dialysis.

Similar reactions have been observed during low-density lipoprotein apheresis with dextran sulphate. This method should, therefore, not be used in patients treated with ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renal disease, may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when Ramipril is given, in particular concomitantly with a diuretic. Dosage reduction of Ramipril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, there is a risk of hyperkalaemia.

Impaired liver function: As ramipril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat, may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).

Symptomatic hypotension: In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of Ramipril as well as after increasing the dose of Ramipril. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with Ramipril.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with Ramipril may usually be continued following restoration of effective blood volume and blood pressure.

Surgery/anaesthesia: In patients undergoing surgery or during anaesthesia with agents producing hypotension, Ramipril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment.

Agranulocytosis and bone marrow depression: In patients on angiotensin converting enzyme inhibitors agranulocytosis and bone marrow depression have been seen rarely, as well as a reduction in red cell count, haemoglobin content and platelet count. These are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and anti metabolites. Patients on allopurinol, immunosuppressants and other substances that may change the blood picture also have increased likelihood of other blood picture changes.

Hyperkalaemia: Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics and the concomitant use of agents to treat hypokalaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to Ramipril. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia. Ramipril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered.
When ACE inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

If Ramipril is given with lithium, an increase in serum lithium concentration may occur.
The protein binding of ramipril is about 73% and of ramiprilat about 56%.

4.6 Pregnancy and lactation

Pregnancy should be excluded before start of treatment with Ramipril and avoided during treatment; exposure of the mother to ACE inhibitors in mid or late pregnancy has been associated with oligohydramnios and neonatal hypotension with anuria or renal failure.

From animal experiments it is known that use of ramipril may cause a decreased utero-placental perfusion. There is also a potential risk of foetal or post-natal effect as ACE inhibitors also influence the local renin-angiotensin system. In peri-post natal studies increased renal pelvic dilatation was observed in the first generation offspring. However, ramipril was not foetotoxic in studies although ACE inhibitors have shown fetotoxicity in some species.

Ramipril should not be used during lactation.

4.7 Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with Raimpril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

Generally, adverse reactions have been mild and transient, and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache.

***Cardiovascular*:** Symptomatic hypotension accompanied by dizziness, weakness and nausea may occur after the initial dose of Ramipril and after an increase in the dose of Ramipril. It has been rarely observed, but may occur in severely salt/volume-depleted patients such as those treated with diuretics, patients on dialysis and in patients with severe congestive heart failure. Syncope has also been observed rarely.

Myocardial infarction or cerebrovascular accident possibly secondary to severe hypotension in high risk patients, chest pain, palpitations, rhythm disturbances, angina pectoris may occur.

Renal: Treatment with Ramipril may impair renal function.

***Gastrointestinal*:** Treatment with Ramipril may be associated with symptoms in the digestive tract, e.g. dryness of the mouth, irritation or inflammation of the oral mucosa, digestive disturbances, constipation, diarrhoea, nausea, and vomiting, (gastritis-like) stomach pain, upper abdominal discomfort (sometimes with increased levels of pancreatic enzymes), increases in hepatic enzymes and/or serum bilirubin, jaundice due to impaired excretion of bile pigment (cholestatic jaundice), other forms of impaired liver function, and hepatitis.

Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

***Allergic*:** Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of Ramipril.
In addition, the following cutaneous and mucosal reactions may occur: reddening of skin areas with accompanying heat sensation, conjunctivitis, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exanthema and enanthema, erythema multiforme), sometimes pronounced hair loss, and precipitation or intensification of Raynaud's phenomenon. With other ACE inhibitors psoriasiform and pemphigoid exanthema and enanthema, hypersensitivity of the skin to light and onycholysis have been observed.
Vasculitis, muscle and joint pains, fever, or eosinophilia may occur. Raised titres of antinuclear antibodies have been seen with other ACE inhibitors.

***Angioneurotic oedema*:** In very rare cases angioneurotic oedema has occurred during therapy with ACE inhibitors including Ramipril. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with Ramipril must be discontinued and appropriate therapy instituted immediately.

Respiratory tract: A dry tickling cough may occur. This is possibly due to the desired ACE inhibition as are the following adverse effects: rhinitis, sinusitis, bronchitis and, especially in patients with tickling cough, bronchospasm.

***Other adverse reactions*:** Disturbances of balance, headache, nervousness, restlessness, tremor, sleep disorders, confusion, loss of appetite, depressed mood, feeling of anxiety, paraesthesiae, taste change, taste reduction and sometimes loss of taste, muscle cramps, erectile impotence and reduced sexual desire may occur.

Laboratory test findings: Increases in blood urea nitrogen and serum creatinine may occur, in particular with renal insufficiency or in patients pretreated with a diuretic. Pre-existing proteinuria may deteriorate.

Serum sodium levels may decrease. Elevation of serum potassium may occur, since Ramipril leads to a decrease in aldosterone secretion; potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements should therefore be avoided.

4.9 Overdose

In case of overdosage prolonged hypotension is to be expected. Treatment with an intravenous infusion of physiological saline and/or angiotensin II may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C09A A05, converting enzyme inhibitor

Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active angiotensin converting enzyme (ACE) inhibitor, ramiprilat which is a potent and long acting ACE inhibitor. Administration of ramipril causes an increase in plasma renin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance. There is evidence suggesting that tissue ACE particularly in the vasculature, rather than circulating ACE, is the primary factor determining the haemodynamic effects.

Angiotensin converting enzyme is identical with kininase II, one of the enzymes responsible for the degradation of bradykinin. There is evidence that ACE inhibition by ramipril appears to have some effects on the kallikrein-kinin-prostaglandin systems. It is assumed that effects on these systems contribute to the hypotensive activity of ramipril.

Administration of Ramipril to hypertensive patients results in reduction of both supine and standing blood pressure. The antihypertensive effect is evident within one to two hours after the drug intake; peak effect occurs 3 - 6 hours after drug intake and has been shown to be maintained for at least 24 hours after therapeutic doses.

In a large endpoint study – HOPE - ramipril significantly reduced the incidence of stroke, myocardial infarction and/or cardiovascular death when compared with placebo. These benefits occurred largely in normotensive patients and were shown, using standard
regression analysis techniques, to be only partially due to the relatively modest reductions in blood pressure demonstrated in the study. The 10mg dose, currently the highest safe dose level approved, was selected by the HOPE investigators from previous dose-ranging studies (SECURE, HEART) and was considered to be the most likely dose to effect full blockade of the renin-angiotensin-aldosterone system. This and other studies suggest that ACE inhibitors like ramipril are likely to have other direct effects on the cardiovascular system. These may include the antagonism of angiotensin II mediated vasoconstriction, the inhibition of proliferating vascular smooth muscle and plaque rupture, the enhancement of endothelial function, the reduction of LV hypertrophy and positive effects on fibrinolysis. Additional effects in diabetic patients may also contribute e.g. effects on insulin clearance and pancreatic blood flow.

5.2 Pharmacokinetic properties

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of ramipril are reached within one hour. Peak plasma concentrations of the active metabolite, ramiprilat, are reached within 2 – 4 hours.

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13 – 17 hours for 5 – 10 mg ramipril and markedly longer for lower doses, 1.25 – 2.5 mg ramipril. This difference is related to the long terminal phase of the ramiprilat concentration time curve observed at very low plasma concentrations. This terminal phase is independent of the dose, indicating a saturable capacity of the enzyme to bind ramiprilat. Steady-state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. In addition to the bioactive metabolite, ramiprilat, other, inactive metabolites have been identified, including diketopiperazine ester, diketopiperazine acid and conjugates.

5.3 Preclinical safety data

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties. Fertility was not impaired either in male or in female rats. The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight and higher.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Lactose monohydrate
Croscarmellose sodium
Pregelatinised starch
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25 °C.
Store in the original package.

6.5 Nature and contents of container

AL/AL Blister packs

Pack sizes: 7, 14, 21, 28, 30, 50, 100 tablets
*not all pack sizes are marketed

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Endwell Limited
Elm House, Ashbourne Industrial Estate
Ashbourne
County Meath
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 18866/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/04/2006

10 DATE OF REVISION OF THE TEXT

05/04/2006

RAMIPRIL 2.5 MG TABLETS (RAMIPRIL)
PL 18843/0015

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 2.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ramipril, 2.5 mg
For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
Light yellow, capsule shaped, uncoated, flat tablet, scored on one side and side walls, marked R2

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Also for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings:

- hypertension (systolic blood pressure > 160mmHg or diastolic blood
- pressure > 90mmHg);
- high total cholesterol (>5.2 mmol/L);
- low HDL (<0.9 mmol/L);
- current smoker;
- known microalbuminuria;
- clinical evidence of previous vascular disease.

Ramipril Tablets are indicated for the treatment of mild to moderate hypertension.

Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

Ramipril Tablets have been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure.

4.2 Posology and method of administration

Oral administration.

Dosage and Administration:

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures: The recommended initial dose is 2.5 mg Ramipril once a day. Depending on the tolerability, the dose should be gradually increased. Therefore, it is recommended that this dose is doubled after about one week of treatment then, after a further 3 weeks, it should be finally increased to 10 mg. The usual maintenance dose is 10 mg Ramipril once a day. Patients already stabilised on lower doses of Ramipril for other indications where possible should be titrated to 10 mg Ramipril once a day.

***Hypertension*:**The recommended initial dose in patients not on diuretics and without congestive heart failure is 1.25 mg Ramipril once a day. Dosage should be increased incrementally at intervals of 1 - 2 weeks, based on patient response, up to a maximum of 10 mg once a day.
A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5 -5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg Ramipril, combination treatment is recommended.
In diuretic treated patients, the diuretic should be discontinued 2 - 3 days before beginning therapy with Ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required.
In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25 mg under close medical supervision in hospital.

***Congestive heart failure*:** The recommended initial dose in patients stabilised on diuretic therapy the initial dose is 1.25 mg once a day. Depending on the patient's response, the dose may be increased. If the dose is increased it is recommended that it is doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. The maximum permitted daily dose is 10 mg.
In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting Ramipril treatment.

Post myocardial infarction: Treatment must be started in hospital between day 3 and day 10 following acute myocardial infarction. The starting dose is 2.5 mg twice a day which is increased to 5 mg twice a day after 2 days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5.0 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day, treatment should be withdrawn.
The maintenance dose is 2.5 to 5.0 mg twice a day.
***Dosage adjustment in renal impairment*:** The usual dose of Ramipril is recommended for patients with a creatinine clearance > 30 ml/min (serum creatinine < 165 µmol/l). For patients with a creatinine clearance < 30 ml/min (serum creatinine >165 µmol/l) the initial dose is 1.25 mg Ramipril once a day and the maximum dose 5 mg Ramipril once a day.
In patients with severe renal impairment (creatinine clearance < 10 ml/min and serum creatinine of 400-650 µmol/l), the recommended initial dose is also 1.25 mg Ramipril once a day, but the maintenance dose should not exceed 2.5 mg Ramipril once a day.

***Dosage in hepatic impairment*:** In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg under close medical supervision in patients with impaired liver function.

***Elderly*:** Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

***Children*:** Ramipril has not been studied in children, and therefore use in this age group is not recommended.

Ramipril tablets should be taken with a glass of water. The absorption of ramipril is not affected by food.

4.3 Contraindications

Hypersensitivity to ramipril or any of the excipients. History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients. Pregnancy. Lactation.

4.4 Special warnings and precautions for use

***Warnings*:**

Ramipril should not be used in patients with aortic or mitral valve stenosis or outflow obstruction.

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

***Precautions*:**

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

Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of Ramipril; their renal function should be closely monitored. In the majority, renal function will not alter. There is a risk of impairment of renal function, particularly in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal artery stenosis in the single kidney as well as after renal transplantation. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

Patients haemodialysed using high flux polyacrylonitrile ('AN69') membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for dialysis. Similar reactions have been observed during low-density lipoprotein apheresis with dextran sulphate. This method should, therefore, not be used in patients treated with ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renal disease, may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when Ramipril is given, in particular concomitantly with a diuretic. Dosage reduction of Ramipril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, there is a risk of hyperkalaemia.

Impaired liver function: As ramipril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat,

may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).

Symptomatic hypotension: In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of Ramipril as well as after increasing the dose of Ramipril. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with Ramipril.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with Ramipril may usually be continued following restoration of effective blood volume and blood pressure.

Surgery/anaesthesia: In patients undergoing surgery or during anaesthesia with agents producing hypotension, Ramipril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment.
Agranulocytosis and bone marrow depression: In patients on angiotensin converting enzyme inhibitors agranulocytosis and bone marrow depression have been seen rarely, as well as a reduction in red cell count, haemoglobin content and platelet count. These are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and anti metabolites. Patients on allopurinol, immunosuppressants and other substances that may change the blood picture also have increased likelihood of other blood picture changes.

Hyperkalaemia: Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics and the concomitant use of agents to treat hypokalaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to Ramipril. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia. Ramipril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered.
When ACE inhibitors are administered simultaneously with non-steroidal antiinflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

If Ramipril is given with lithium, an increase in serum lithium concentration may occur.

The protein binding of ramipril is about 73% and of ramiprilat about 56%.

4.6 Pregnancy and lactation

Pregnancy should be excluded before start of treatment with Ramipril and avoided during treatment; exposure of the mother to ACE inhibitors in mid or late pregnancy has been associated with oligohydramnios and neonatal hypotension with anuria or renal failure.

From animal experiments it is known that use of ramipril may cause a decreased utero-placental perfusion. There is also a potential risk of foetal or post-natal effect as ACE inhibitors also influence the local renin-angiotensin system. In peri-post natal studies increased renal pelvic dilatation was observed in the first generation offspring. However, ramipril was not foetotoxic in studies although ACE inhibitors have shown fetotoxicity in some species.

Ramipril should not be used during lactation.

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In individual cases, as a result of a reduction in blood pressure, treatment with Raimpril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

Generally, adverse reactions have been mild and transient, and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache.

***Cardiovascular*:** Symptomatic hypotension accompanied by dizziness, weakness and nausea may occur after the initial dose of Ramipril and after an increase in the dose of Ramipril. It has been rarely observed, but may occur in severely salt/volume-depleted patients such as those treated with diuretics, patients on dialysis and in patients with severe congestive heart failure. Syncope has also been observed rarely.

Myocardial infarction or cerebrovascular accident possibly secondary to severe hypotension in high risk patients, chest pain, palpitations, rhythm disturbances, angina pectoris may occur.

Renal: Treatment with Ramipril may impair renal function.

***Gastrointestinal*:** Treatment with Ramipril may be associated with symptoms in the digestive tract, e.g. dryness of the mouth, irritation or inflammation of the oral mucosa, digestive disturbances, constipation, diarrhoea, nausea, and vomiting, (gastritis-like) stomach pain, upper abdominal discomfort (sometimes with increased levels of pancreatic enzymes), increases in hepatic enzymes and/or serum bilirubin, jaundice due to impaired excretion of bile pigment (cholestatic jaundice), other forms of impaired liver function, and hepatitis.

Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in

some cases this has proved fatal.

***Allergic*:** Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of Ramipril.
In addition, the following cutaneous and mucosal reactions may occur: reddening of skin areas with accompanying heat sensation, conjunctivitis, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exanthema and enanthema, erythema multiforme), sometimes pronounced hair loss, and precipitation or intensification of Raynaud's phenomenon. With other ACE inhibitors psoriasiform and pemphigoid exanthema and enanthema, hypersensitivity of the skin to light and onycholysis have been observed.
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Respiratory tract: A dry tickling cough may occur. This is possibly due to the desired ACE inhibition as are the following adverse effects: rhinitis, sinusitis, bronchitis and, especially in patients with tickling cough, bronchospasm.

***Other adverse reactions*:** Disturbances of balance, headache, nervousness, restlessness, tremor, sleep disorders, confusion, loss of appetite, depressed mood, feeling of anxiety, paraesthesiae, taste change, taste reduction and sometimes loss of taste, muscle cramps, erectile impotence and reduced sexual desire may occur.

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Serum sodium levels may decrease. Elevation of serum potassium may occur, since Ramipril leads to a decrease in aldosterone secretion; potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements should therefore be avoided.

4.9 Overdose

In case of overdosage prolonged hypotension is to be expected. Treatment with an intravenous infusion of physiological saline and/or angiotensin II may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C09A A05, converting enzyme inhibitor.

Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active angiotensin converting enzyme (ACE) inhibitor, ramiprilat which is a potent and long acting ACE inhibitor. Administration of ramipril causes an increase in plasma renin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance. There is evidence suggesting that

tissue ACE particularly in the vasculature, rather than circulating ACE, is the primary factor determining the haemodynamic effects.

Angiotensin converting enzyme is identical with kininase II, one of the enzymes responsible for the degradation of bradykinin. There is evidence that ACE inhibition by ramipril appears to have some effects on the kallikreinkinin-prostaglandin systems. It is assumed that effects on these systems contribute to the hypotensive activity of ramipril.

Administration of Ramipril to hypertensive patients results in reduction of both supine and standing blood pressure. The antihypertensive effect is evident within one to two hours after the drug intake; peak effect occurs 3 - 6 hours after drug intake and has been shown to be maintained for at least 24 hours after therapeutic doses.

In a large endpoint study – HOPE - ramipril significantly reduced the incidence of stroke, myocardial infarction and/or cardiovascular death when compared with placebo. These benefits occurred largely in normotensive patients and were shown, using standard regression analysis techniques, to be only partially due to the relatively modest reductions in blood pressure demonstrated in the study. The 10mg dose, currently the highest safe dose level approved, was selected by the HOPE investigators from previous doseranging studies (SECURE, HEART) and was considered to be the most likely dose to effect full blockade of the renin-angiotensin-aldosterone system. This and other studies suggest that ACE inhibitors like ramipril are likely to have other direct effects on the cardiovascular system. These may include the antagonism of angiotensin II mediated vasoconstriction, the inhibition of proliferating vascular smooth muscle and plaque rupture, the enhancement of endothelial function, the reduction of LV hypertrophy and positive effects on fibrinolysis. Additional effects in diabetic patients may also contribute e.g. effects on insulin clearance and pancreatic blood flow.

5.2 Pharmacokinetic properties

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of ramipril are reached within one hour. Peak plasma concentrations of the active metabolite, ramiprilat, are reached within 2 – 4 hours.

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13 – 17 hours for 5 – 10 mg ramipril and markedly longer for lower doses, 1.25 – 2.5 mg ramipril. This difference is related to the long terminal phase of the ramiprilat concentration time curve observed at very low plasma concentrations. This terminal phase is independent of the dose, indicating a saturable capacity of the enzyme to bind ramiprilat. Steady-state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. In addition to the bioactive metabolite, ramiprilat, other, inactive metabolites have been identified, including diketopiperazine ester, diketopiperazine acid and conjugates.

5.3 Preclinical safety data

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties. Fertility was not impaired either in male or in female rats. The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal

pelvis) in the offspring at daily doses of 50 mg/kg body weight and higher.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Lactose monohydrate
Croscarmellose sodium
Pregelatinised starch
Sodium stearyl fumarate
Yellow Iron Oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25 °C.
Store in the original package.

6.5 Nature and contents of container

AL/AL Blister packs

Pack sizes: 7, 14, 21, 28, 30, 50, 100 tablets
*not all pack sizes are marketed

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Endwell Limited
Elm House, Ashbourne Industrial Estate
Ashbourne
County Meath
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 18866/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/04/2006

10 DATE OF REVISION OF THE TEXT

05/04/2006

RAMIPRIL 5 MG TABLETS (RAMIPRIL)
PL 18843/0016

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ramipril, 5 mg
For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
Light pink, capsule shaped, uncoated, flat tablet, scored on one side and side walls, marked R3

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Also for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings:

- hypertension (systolic blood pressure > 160mmHg or diastolic blood
- pressure > 90mmHg);
- high total cholesterol (>5.2 mmol/L);
- low HDL (<0.9 mmol/L);
- current smoker;
- known microalbuminuria;
- clinical evidence of previous vascular disease.
-

Ramipril Tablets are indicated for the treatment of mild to moderate hypertension.

Congestive heart failure as adjunctive therapy to diuretics with or without cardiac glycosides.

Ramipril Tablets have been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure.

4.2 Posology and method of administration

Oral administration.

Dosage and Administration:

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures: The recommended initial dose is 2.5 mg Ramipril once a day. Depending on the tolerability, the dose should be gradually increased. Therefore, it is recommended that this dose is doubled after about one week of treatment then, after a further 3 weeks, it should be finally increased to 10 mg. The usual maintenance dose is 10 mg Ramipril once a day. Patients already stabilised on lower doses of Ramipril for other indications where possible should be titrated to 10 mg Ramipril once a day.

***Hypertension*:**The recommended initial dose in patients not on diuretics and without congestive heart failure is 1.25 mg Ramipril once a day. Dosage should be increased incrementally at intervals of 1 - 2 weeks, based on patient response, up to a maximum of 10 mg once a day.

A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5 -5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg Ramipril, combination treatment is recommended.

In diuretic treated patients, the diuretic should be discontinued 2 - 3 days before beginning therapy with Ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required.

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25 mg under close medical supervision in hospital.

***Congestive heart failure*:** The recommended initial dose in patients stabilised on diuretic therapy the initial dose is 1.25 mg once a day. Depending on the patient's response, the dose may be increased. If the dose is increased it is recommended that it is doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. The maximum permitted daily dose is 10 mg.

In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting Ramipril treatment.

Post myocardial infarction: Treatment must be started in hospital between day 3 and day 10 following acute myocardial infarction. The starting dose is 2.5 mg twice a day which is increased to 5 mg twice a day after 2 days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5.0 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day, treatment should be withdrawn.
The maintenance dose is 2.5 to 5.0 mg twice a day.

***Dosage adjustment in renal impairment*:** The usual dose of Ramipril is recommended for patients with a creatinine clearance > 30 ml/min (serum creatinine < 165 µmol/l). For patients with a creatinine clearance < 30 ml/min (serum creatinine >165 µmol/l) the initial dose is 1.25 mg Ramipril once a day and the maximum dose 5 mg Ramipril once a day.
In patients with severe renal impairment (creatinine clearance < 10 ml/min and serum creatinine of 400-650 µmol/l), the recommended initial dose is also 1.25 mg Ramipril once a day, but the maintenance dose should not exceed 2.5 mg Ramipril once a day.

***Dosage in hepatic impairment*:** In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg under close medical supervision in patients with impaired liver function.

***Elderly*:** Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

***Children*:** Ramipril has not been studied in children, and therefore use in this age group is not recommended.
Ramipril tablets should be taken with a glass of water. The absorption of ramipril is not affected by food.

4.3 Contraindications

Hypersensitivity to ramipril or any of the excipients. History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients. Pregnancy. Lactation.

4.4 Special warnings and precautions for use

***Warnings*:**

Ramipril should not be used in patients with aortic or mitral valve stenosis or outflow obstruction.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
***Precautions*:**

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

Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of Ramipril; their renal function should be closely monitored. In the majority, renal function will not alter. There is a risk of impairment of renal function, particularly in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal artery stenosis in the single kidney as well as after renal transplantation. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

Patients haemodialysed using high flux polyacrylonitrile ('AN69') membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for dialysis.

Similar reactions have been observed during low-density lipoprotein apheresis with dextran sulphate. This method should, therefore, not be used in patients treated with ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renal disease, may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when Ramipril is given, in particular concomitantly with a diuretic. Dosage reduction of Ramipril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, there is a

risk of hyperkalaemia.

Impaired liver function: As ramipril is a prodrug metabolised to its active moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat, may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).

Symptomatic hypotension: In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of Ramipril as well as after increasing the dose of Ramipril. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with Ramipril.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with Ramipril may usually be continued following restoration of effective blood volume and blood pressure.

Surgery/anaesthesia: In patients undergoing surgery or during anaesthesia with agents producing hypotension, Ramipril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment.

Agranulocytosis and bone marrow depression: In patients on angiotensin converting enzyme inhibitors agranulocytosis and bone marrow depression have been seen rarely, as well as a reduction in red cell count, haemoglobin content and platelet count. These are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and anti metabolites. Patients on allopurinol, immunosuppressants and other substances that may change the blood picture also have increased likelihood of other blood picture changes.

Hyperkalaemia: Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics and the concomitant use of agents to treat hypokalaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to Ramipril. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia. Ramipril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered.
When ACE inhibitors are administered simultaneously with non-steroidal antiinflammatory drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

If Ramipril is given with lithium, an increase in serum lithium concentration may occur.

The protein binding of ramipril is about 73% and of ramiprilat about 56%.

4.6 Pregnancy and lactation

Pregnancy should be excluded before start of treatment with Ramipril and avoided during treatment; exposure of the mother to ACE inhibitors in mid or late pregnancy has been associated with oligohydramnios and neonatal hypotension with anuria or renal failure.

From animal experiments it is known that use of ramipril may cause a decreased utero-placental perfusion. There is also a potential risk of foetal or post-natal effect as ACE inhibitors also influence the local renin-angiotensin system. In peri-post natal studies increased renal pelvic dilatation was observed in the first generation offspring. However, ramipril was not foetotoxic in studies although ACE inhibitors have shown fetotoxicity in some species.

Ramipril should not be used during lactation.

4.7 Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with Raimpril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

Generally, adverse reactions have been mild and transient, and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache.

***Cardiovascular*:** Symptomatic hypotension accompanied by dizziness, weakness and nausea may occur after the initial dose of Ramipril and after an increase in the dose of Ramipril. It has been rarely observed, but may occur in severely salt/volume-depleted patients such as those treated with diuretics, patients on dialysis and in patients with severe congestive heart failure.
Syncope has also been observed rarely.
Myocardial infarction or cerebrovascular accident possibly secondary to severe hypotension in high risk patients, chest pain, palpitations, rhythm disturbances, angina pectoris may occur.

Renal: Treatment with Ramipril may impair renal function.

***Gastrointestinal*:** Treatment with Ramipril may be associated with symptoms in the digestive tract, e.g. dryness of the mouth, irritation or inflammation of the oral mucosa, digestive disturbances, constipation, diarrhoea, nausea, and vomiting, (gastritis-like) stomach pain, upper abdominal discomfort

(sometimes with increased levels of pancreatic enzymes), increases in hepatic enzymes and/or serum bilirubin, jaundice due to impaired excretion of bile pigment (cholestatic jaundice), other forms of impaired liver function, and hepatitis.

Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

***Allergic*:** Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of Ramipril.
In addition, the following cutaneous and mucosal reactions may occur: reddening of skin areas with accompanying heat sensation, conjunctivitis, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exanthema and enanthema, erythema multiforme), sometimes pronounced hair loss, and precipitation or intensification of Raynaud's phenomenon. With other ACE inhibitors psoriasiform and pemphigoid exanthema and enanthema, hypersensitivity of the skin to light and onycholysis have been observed.
Vasculitis, muscle and joint pains, fever, or eosinophilia may occur. Raised titres of antinuclear antibodies have been seen with other ACE inhibitors.

***Angioneurotic oedema*:** In very rare cases angioneurotic oedema has occurred during therapy with ACE inhibitors including Ramipril. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with Ramipril must be discontinued and appropriate therapy instituted immediately.

Respiratory tract: A dry tickling cough may occur. This is possibly due to the desired ACE inhibition as are the following adverse effects: rhinitis, sinusitis, bronchitis and, especially in patients with tickling cough, bronchospasm.

***Other adverse reactions*:** Disturbances of balance, headache, nervousness, restlessness, tremor, sleep disorders, confusion, loss of appetite, depressed mood, feeling of anxiety, paraesthesiae, taste change, taste reduction and sometimes loss of taste, muscle cramps, erectile impotence and reduced sexual desire may occur.

Laboratory test findings: Increases in blood urea nitrogen and serum creatinine may occur, in particular with renal insufficiency or in patients pretreated with a diuretic. Pre-existing proteinuria may deteriorate.
Serum sodium levels may decrease. Elevation of serum potassium may occur, since Ramipril leads to a decrease in aldosterone secretion; potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements should therefore be avoided.

4.9 Overdose

In case of overdosage prolonged hypotension is to be expected. Treatment with an intravenous infusion of physiological saline and/or angiotensin II may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C09A A05, converting enzyme inhibitor.

Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active angiotensin converting enzyme (ACE) inhibitor, ramiprilat which is a potent and long acting ACE inhibitor.

Administration of ramipril causes an increase in plasma renin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance. There is evidence suggesting that tissue ACE particularly in the vasculature, rather than circulating ACE, is the primary factor determining the haemodynamic effects.

Angiotensin converting enzyme is identical with kininase II, one of the enzymes responsible for the degradation of bradykinin. There is evidence that ACE inhibition by ramipril appears to have some effects on the kallikreinkinin-prostaglandin systems. It is assumed that effects on these systems contribute to the hypotensive activity of ramipril.

Administration of Ramipril to hypertensive patients results in reduction of both supine and standing blood pressure. The antihypertensive effect is evident within one to two hours after the drug intake; peak effect occurs 3 - 6 hours after drug intake and has been shown to be maintained for at least 24 hours after therapeutic doses.

In a large endpoint study – HOPE - ramipril significantly reduced the incidence of stroke, myocardial infarction and/or cardiovascular death when compared with placebo. These benefits occurred largely in normotensive patients and were shown, using standard regression analysis techniques, to be only partially due to the relatively modest reductions in blood pressure demonstrated in the study. The 10mg dose, currently the highest safe dose level approved, was selected by the HOPE investigators from previous dose-ranging studies (SECURE, HEART) and was considered to be the most likely dose to effect full blockade of the reninangiotensin-aldosterone system. This and other studies suggest that ACE inhibitors like ramipril are likely to have other direct effects on the cardiovascular system. These may include the antagonism of angiotensin II mediated vasoconstriction, the inhibition of proliferating vascular smooth muscle and plaque rupture, the enhancement of endothelial function, the reduction of LV hypertrophy and positive effects on fibrinolysis. Additional effects in diabetic patients may also contribute e.g. effects on insulin clearance and pancreatic blood flow.

5.2 Pharmacokinetic properties

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of ramipril are reached within one hour. Peak plasma concentrations of the active metabolite, ramiprilat, are reached within 2 – 4 hours.

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13 – 17 hours for 5 – 10 mg ramipril and markedly longer for lower doses, 1.25 – 2.5 mg ramipril. This difference is related to the long terminal phase of the ramiprilat concentration time curve observed at very low plasma concentrations. This terminal phase is independent of the dose, indicating a saturable capacity of the enzyme to bind ramiprilat. Steady-state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. In addition to the bioactive metabolite, ramiprilat, other, inactive metabolites have been identified, including diketopiperazine ester, diketopiperazine acid and conjugates.

5.3 Preclinical safety data

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties. Fertility was not impaired either in male or in female rats. The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight and higher.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Lactose monohydrate
Croscarmellose sodium
Pregelatinised starch
Sodium stearyl fumarate
Yellow Iron Oxide (E172)
Red Iron Oxide (E172)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.3. Special precautions for storage

Do not store above 25 °C.
Store in the original package.

6.5 Nature and contents of container

AL/AL Blister packs

Pack sizes: 7, 14, 21, 28, 30, 50, 100 tablets
*not all pack sizes are marketed

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Endwell Limited
Elm House, Ashbourne Industrial Estate
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County Meath
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8 MARKETING AUTHORISATION NUMBER(S)

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RAMIPRIL 10 MG TABLETS (RAMIPRIL)
PL 18843/0017

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ramipril 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ramipril, 10 mg

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
White, capsule shaped, uncoated, flat tablet, scored on one side and side walls.
Marked R4

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in patients of 55 years or more who have clinical evidence of cardiovascular disease (previous MI, unstable angina or multivessel CABG or multivessel PTCA), stroke or peripheral vascular disease.

Also for reducing the risk of myocardial infarction, stroke, cardiovascular death or need for revascularisation procedures in diabetic patients of 55 years or more who have one or more of the following clinical findings:

- hypertension (systolic blood pressure > 160mmHg or diastolic blood pressure > 90mmHg);
- high total cholesterol (>5.2 mmol/L);
- low HDL (<0.9 mmol/L);
- current smoker;
- known microalbuminuria;
- clinical evidence of previous vascular disease.
- Ramipril Tablets are indicated for the treatment of mild to moderate
- hypertension.
- Congestive heart failure as adjunctive therapy to diuretics with or without
- cardiac glycosides.

Ramipril Tablets have been shown to reduce mortality when given to patients surviving acute myocardial infarction with clinical evidence of heart failure.

4.2 Posology and method of administration

Oral administration.

Dosage and Administration:

Reducing the risk of myocardial infarction, stroke or cardiovascular death and/or the need for revascularisation procedures: The recommended initial dose is 2.5 mg Ramipril once a day. Depending on the tolerability, the dose should be gradually increased. Therefore, it is recommended that this dose is doubled after about one week of treatment then, after a further 3 weeks, it should be finally increased to 10 mg. The usual maintenance dose is 10 mg Ramipril once a day. Patients already stabilised on lower doses of Ramipril for other indications where possible should be titrated to 10 mg Ramipril once a day.

***Hypertension*:**The recommended initial dose in patients not on diuretics and without congestive heart failure is 1.25 mg Ramipril once a day. Dosage should be increased incrementally at intervals of 1 - 2 weeks, based on patient response, up to a maximum of 10 mg once a day.

A 1.25 mg dose will only achieve a therapeutic response in a minority of patients. The usual maintenance dose is 2.5 -5 mg as a single daily dose. If the patient response is still unsatisfactory at a dose of 10 mg Ramipril, combination treatment is recommended.

In diuretic treated patients, the diuretic should be discontinued 2 - 3 days before beginning therapy with Ramipril to reduce the likelihood of symptomatic hypotension. It may be resumed later if required.

In hypertensive patients who also have congestive heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed after treatment with ACE inhibitors. In these patients therapy should be started at a dose of 1.25 mg under close medical supervision in hospital.

***Congestive heart failure*:** The recommended initial dose in patients stabilised on diuretic therapy the initial dose is 1.25 mg once a day. Depending on the patient's response, the dose may be increased. If the dose is increased it is recommended that it is doubled at intervals of 1 to 2 weeks. If a daily dose of 2.5 mg or more is required, this may be taken as a single dose or as two divided doses. The maximum permitted daily dose is 10 mg.

In order to minimise the possibility of symptomatic hypotension, patients on previous high dose diuretics should have the diuretic dose reduced before starting Ramipril treatment.

Post myocardial infarction: Treatment must be started in hospital between day 3 and day 10 following acute myocardial infarction. The starting dose is 2.5 mg twice a day which is increased to 5 mg twice a day after 2 days. If the initial 2.5 mg dose is not tolerated a dose of 1.25 mg twice a day should be given for two days before increasing to 2.5 mg and 5.0 mg twice a day. If the dose cannot be increased to 2.5 mg twice a day, treatment should be withdrawn.
The maintenance dose is 2.5 to 5.0 mg twice a day.

***Dosage adjustment in renal impairment*:** The usual dose of Ramipril is recommended for patients with a creatinine clearance > 30 ml/min (serum creatinine < 165 μmol/l). For patients with a creatinine clearance < 30 ml/min (serum creatinine >165 μmol/l) the initial dose is 1.25 mg Ramipril once a day and the maximum dose 5 mg Ramipril once a day.
In patients with severe renal impairment (creatinine clearance < 10 ml/min and serum creatinine of 400-650 μmol/l), the recommended initial dose is also 1.25 mg Ramipril once a day, but the maintenance dose should not exceed 2.5 mg Ramipril once a day.
***Dosage in hepatic impairment*:** In patients with impaired liver function the metabolism of the parent compound ramipril, and therefore the formation of

the bioactive metabolite ramiprilat, is delayed due to a diminished activity of esterases in the liver, resulting in elevated plasma ramipril levels. Treatment with ramipril should therefore be initiated at a dose of 1.25 mg under close medical supervision in patients with impaired liver function.

***Elderly*:** Caution in elderly patients with concomitant use of diuretics, congestive heart failure or renal or hepatic insufficiency. The dose should be titrated according to need for the control of blood pressure.

***Children*:** Ramipril has not been studied in children, and therefore use in this age group is not recommended.

Ramipril tablets should be taken with a glass of water. The absorption of ramipril is not affected by food.

4.3 Contraindications

Hypersensitivity to ramipril or any of the excipients. History of angioneurotic oedema, haemodynamically relevant renal artery stenosis, hypotensive or haemodynamically unstable patients. Pregnancy. Lactation.

4.3 Special warnings and precautions for use

***Warnings*:**

Ramipril should not be used in patients with aortic or mitral valve stenosis or outflow obstruction.

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

***Precautions*:**

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

Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of Ramipril; their renal function should be closely monitored. In the majority, renal function will not alter. There is a risk of impairment of renal function, particularly in patients with renal insufficiency, congestive heart failure, bilateral renal artery stenosis and unilateral renal artery stenosis in the single kidney as well as after renal transplantation. If recognised early, such impairment of renal function is reversible upon discontinuation of therapy.

Patients haemodialysed using high flux polyacrylonitrile ('AN69') membranes are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes for dialysis. Similar reactions have been observed during low-density lipoprotein apheresis with dextran sulphate. This method should, therefore, not be used in patients treated with ACE inhibitors.

Some hypertensive patients with no apparent pre-existing renal disease, may develop minor and usually transient increases in blood urea nitrogen and serum creatinine when Ramipril is given, in particular concomitantly with a diuretic. Dosage reduction of Ramipril and/or discontinuation of the diuretic may be required. Additionally, in patients with renal insufficiency, there is a risk of hyperkalaemia.

Impaired liver function: As ramipril is a prodrug metabolised to its active

moiety in the liver, particular caution and close monitoring should be applied to patients with impaired liver function. The metabolism of the parent compound, and therefore the formation of the bioactive metabolite ramiprilat, may be diminished resulting in markedly elevated plasma levels of the parent compound (due to the reduced activity of esterases in the liver).

Symptomatic hypotension: In patients with uncomplicated hypertension, symptomatic hypotension has been observed rarely after the initial dose of Ramipril as well as after increasing the dose of Ramipril. It is more likely to occur in patients who have been volume- and salt-depleted by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, vomiting or patients with severe heart failure. Therefore, in these patients, diuretic therapy should be discontinued and volume and/or salt depletion should be corrected before initiating therapy with Ramipril.

If symptomatic hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of physiological saline. Intravenous atropine may be necessary if there is associated bradycardia. Treatment with Ramipril may usually be continued following restoration of effective blood volume and blood pressure.

Surgery/anaesthesia: In patients undergoing surgery or during anaesthesia with agents producing hypotension, Ramipril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by appropriate treatment.

Agranulocytosis and bone marrow depression: In patients on angiotensin converting enzyme inhibitors agranulocytosis and bone marrow depression have been seen rarely, as well as a reduction in red cell count, haemoglobin content and platelet count. These are more frequent in patients with renal impairment, especially if they have a collagen vascular disease. Regular monitoring of white blood cell counts and protein levels in urine should be considered in patients with collagen vascular disease (e.g. lupus erythematosus and scleroderma), especially associated with impaired renal function and concomitant therapy particularly with corticosteroids and anti metabolites. Patients on allopurinol, immunosuppressants and other substances that may change the blood picture also have increased likelihood of other blood picture changes.

Hyperkalaemia: Elevated serum potassium has been observed very rarely in hypertensive patients. Risk factors for the development of hyperkalaemia include renal insufficiency, potassium sparing diuretics and the concomitant use of agents to treat hypokalaemia.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with diuretics or other antihypertensive agents may potentiate the antihypertensive response to Ramipril. Adrenergic-blocking drugs should only be combined with ramipril under careful supervision.

Potassium sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements may increase the risk of hyperkalaemia. Ramipril may attenuate the potassium loss caused by thiazide-type diuretics. If concomitant use of these agents is indicated, they should be given with caution and serum potassium should be monitored regularly.

When antidiabetic agents (insulin and sulphonylurea derivatives) are used concurrently, the possibility of increased blood-sugar reduction must be considered.
When ACE inhibitors are administered simultaneously with non-steroidal antiinflammatory

drugs (e.g. acetylsalicylic acid and indomethacin), attenuation of the antihypertensive effect may occur.

If Ramipril is given with lithium, an increase in serum lithium concentration may occur.
The protein binding of ramipril is about 73% and of ramiprilat about 56%

4.6 Pregnancy and lactation

Pregnancy should be excluded before start of treatment with Ramipril and avoided during treatment; exposure of the mother to ACE inhibitors in mid or late pregnancy has been associated with oligohydramnios and neonatal hypotension with anuria or renal failure.

From animal experiments it is known that use of ramipril may cause a decreased utero-placental perfusion. There is also a potential risk of foetal or post-natal effect as ACE inhibitors also influence the local renin-angiotensin system. In peri-post natal studies increased renal pelvic dilatation was observed in the first generation offspring. However, ramipril was not foetotoxic in studies although ACE inhibitors have shown fetotoxicity in some species.

Ramipril should not be used during lactation.

4.7 Effects on ability to drive and use machines

In individual cases, as a result of a reduction in blood pressure, treatment with Raimpril may affect the ability to drive and operate machinery. This occurs especially at the start of treatment, when changing over from other preparations and during concomitant use of alcohol. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

Generally, adverse reactions have been mild and transient, and do not require discontinuation of therapy. The most frequently reported adverse reactions are nausea, dizziness and headache.

***Cardiovascular*:** Symptomatic hypotension accompanied by dizziness, weakness and nausea may occur after the initial dose of Ramipril and after an increase in the dose of Ramipril. It has been rarely observed, but may occur in severely salt/volume-depleted patients such as those treated with diuretics, patients on dialysis and in patients with severe congestive heart failure. Syncope has also been observed rarely.

Myocardial infarction or cerebrovascular accident possibly secondary to severe hypotension in high risk patients, chest pain, palpitations, rhythm disturbances, angina pectoris may occur.

Renal: Treatment with Ramipril may impair renal function.

***Gastrointestinal*:** Treatment with Ramipril may be associated with symptoms in the digestive tract, e.g. dryness of the mouth, irritation or inflammation of the oral mucosa, digestive disturbances, constipation, diarrhoea, nausea, and vomiting, (gastritis-like) stomach pain, upper abdominal discomfort (sometimes with increased levels of pancreatic enzymes), increases in hepatic enzymes and/or serum bilirubin, jaundice due to impaired excretion of bile pigment (cholestatic jaundice), other forms of impaired liver function, and hepatitis.

Pancreatitis has been reported rarely in patients treated with ACE inhibitors; in some cases this has proved fatal.

***Allergic*:** Hypersensitivity reactions accompanied by pruritus, rash, shortness of breath and sometimes fever may occur, but usually resolve spontaneously after withdrawal of Ramipril.
In addition, the following cutaneous and mucosal reactions may occur: reddening of skin areas with accompanying heat sensation, conjunctivitis, itching, urticaria, other skin or mucosal eruptions (maculo-papular and lichenoid exanthema and enanthema, erythema multiforme), sometimes pronounced hair loss, and precipitation or intensification of Raynaud's phenomenon. With other ACE inhibitors psoriasiform and pemphigoid exanthema and enanthema, hypersensitivity of the skin to light and onycholysis have been observed.
Vasculitis, muscle and joint pains, fever, or eosinophilia may occur. Raised titres of antinuclear antibodies have been seen with other ACE inhibitors.

***Angioneurotic oedema*:** In very rare cases angioneurotic oedema has occurred during therapy with ACE inhibitors including Ramipril. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with Ramipril must be discontinued and appropriate therapy instituted immediately.

Respiratory tract: A dry tickling cough may occur. This is possibly due to the desired ACE inhibition as are the following adverse effects: rhinitis, sinusitis, bronchitis and, especially in patients with tickling cough, bronchospasm.

***Other adverse reactions*:** Disturbances of balance, headache, nervousness, restlessness, tremor, sleep disorders, confusion, loss of appetite, depressed mood, feeling of anxiety, paraesthesiae, taste change, taste reduction and sometimes loss of taste, muscle cramps, erectile impotence and reduced sexual desire may occur.

Laboratory test findings: Increases in blood urea nitrogen and serum creatinine may occur, in particular with renal insufficiency or in patients pretreated with a diuretic. Pre-existing proteinuria may deteriorate.
Serum sodium levels may decrease. Elevation of serum potassium may occur, since Ramipril leads to a decrease in aldosterone secretion; potassium-sparing diuretics (spironolactone, amiloride, triamterene) or potassium supplements should therefore be avoided.

4.9 Overdose

In case of overdosage prolonged hypotension is to be expected. Treatment with an intravenous infusion of physiological saline and/or angiotensin II may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C09A A05, converting enzyme inhibitor.
Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active angiotensin converting enzyme (ACE) inhibitor, ramiprilat which is a potent and long acting ACE inhibitor. Administration of ramipril causes an increase in plasma renin activity and a decrease in plasma concentrations of angiotensin II and aldosterone. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance. There is evidence suggesting that tissue ACE particularly in the vasculature, rather than circulating ACE, is the

primary factor determining the haemodynamic effects.
Angiotensin converting enzyme is identical with kininase II, one of the enzymes responsible for the degradation of bradykinin. There is evidence that ACE inhibition by ramipril appears to have some effects on the kallikreinkinin-prostaglandin systems. It is assumed that effects on these systems contribute to the hypotensive activity of ramipril.

Administration of Ramipril to hypertensive patients results in reduction of both supine and standing blood pressure. The antihypertensive effect is evident within one to two hours after the drug intake; peak effect occurs 3 - 6 hours after drug intake and has been shown to be maintained for at least 24 hours after therapeutic doses.
In a large endpoint study – HOPE - ramipril significantly reduced the incidence of stroke, myocardial infarction and/or cardiovascular death when compared with placebo. These benefits occurred largely in normotensive patients and were shown, using standard
regression analysis techniques, to be only partially due to the relatively modest reductions in blood pressure demonstrated in the study. The 10mg dose, currently the highest safe dose level approved, was selected by the HOPE investigators from previous dose-ranging studies (SECURE, HEART) and was considered to be the most likely dose to effect full blockade of the reninangiotensin-aldosterone system. This and other studies suggest that ACE
inhibitors like ramipril are likely to have other direct effects on the cardiovascular system. These may include the antagonism of angiotensin II mediated vasoconstriction, the inhibition of proliferating vascular smooth muscle and plaque rupture, the enhancement of endothelial function, the reduction of LV hypertrophy and positive effects on fibrinolysis. Additional effects in diabetic patients may also contribute e.g. effects on insulin clearance and pancreatic blood flow.

5.2 Pharmacokinetic properties

Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of ramipril are reached within one hour. Peak plasma concentrations of the active metabolite, ramiprilat, are reached within 2 – 4 hours.

Plasma concentrations of ramiprilat decline in a polyphasic manner. The effective half-life of ramiprilat after multiple once daily administration of ramipril is 13 – 17 hours for 5 – 10 mg ramipril and markedly longer for lower doses, 1.25 – 2.5 mg ramipril. This difference is related to the long terminal phase of the ramiprilat concentration time curve observed at very low plasma concentrations. This terminal phase is independent of the dose, indicating a saturable capacity of the enzyme to bind ramiprilat. Steady-state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Ramipril is almost completely metabolised and the metabolites are excreted mainly via the kidneys. In addition to the bioactive metabolite, ramiprilat, other, inactive metabolites have been identified, including diketopiperazine ester, diketopiperazine acid and conjugates.

5.3 Preclinical safety data

Reproduction toxicology studies in the rat, rabbit and monkey did not disclose any teratogenic properties. Fertility was not impaired either in male or in female rats. The administration of ramipril to female rats during the fetal period and lactation produced irreversible renal damage (dilatation of the renal pelvis) in the offspring at daily doses of 50 mg/kg body weight and higher.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Lactose monohydrate
Croscarmellose sodium
Pregelatinised starch
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25 °C.
Store in the original package.

6.5 Nature and contents of container

AL/AL Blister packs
Pack sizes: 7, 14, 21, 28, 30, 50, 100 tablets
*not all pack sizes are marketed

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Endwell Limited
Elm House, Ashbourne Industrial Estate
Ashbourne
County Meath
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 18843/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/04/2006

10 DATE OF REVISION OF THE TEXT

05/04/2006

RAMIPRIL 1.25, 2.5, 5 AND 10MG TABLETS (RAMIPRIL)
PL 18843/0014-17
PRODUCT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET
Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Tablets

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

In this leaflet:

The name of your medicine is Ramipril 1.25 mg, 2.5 mg, 5 mg or 10 mg Tablets

- The active substance in your medicine is ramipril. Ramipril 1.25 mg Tablets are white to off white, oval shaped, flat tablets and contain 1.25 mg ramipril. Ramipril 2.5 mg Tablets are yellow, oval shaped flat tablets scored on one side and side walls. Marked R2 and contain 2.5 mg ramipril. Ramipril 5 mg Tablets are pink oval shaped, flat tablets, scored on one side and side walls. Marked R3 and contain 5 mg ramipril. Ramipril 10 mg Tablets are white to off white, oval shaped, flat tablets scored on one side and side walls. Marked R4 and contain 10 mg ramipril.
- The other ingredients are sodium hydrogen carbonate, lactose monohydrate, croscarmellose sodium, pregelatinised starch and sodium stearyl fumarate. The 2.5 mg and 5mg tablets also contain yellow iron oxide and the 5 mg tablets also contain red iron oxide.
- The tablets are supplied in blister packs and bottles of 7, 14, 21, 28, 30, 50 and 100 tablets.*

* only marketed pack sizes are stated

Ramipril tablets are manufactured by Actavis Limited, Reykjavikurvegur 78, IS-220 Hafnarfjordur, Iceland.

The Marketing Authorisation Holder is Endwell Limited, Elm House, Ashbourne Industrial Estate, Ashbourne, County Meath, Ireland.

1. WHAT RAMIPRIL TABLETS ARE AND WHAT THEY ARE USED FOR

Ramipril belongs to a group of medicines called ACE (angiotensin converting enzyme) inhibitors which reduce blood pressure and help your heart pump blood around your body. It can also help the heart to work better if the heart does not pump as well as is needed.

Your doctor has probably prescribed Ramipril Tablets for one or more of the following reasons:
- To help lower your blood pressure if it is mild to moderately high.
- You have a heart condition, congestive heart failure which means the heart isn't working as well as it did. Ramipril will help your heart to pump the blood around your body. Ramipril Tablets are taken as additional medication with water tablets.
- To help prevent your heart from weakening further if you have had a heart attack.
- In patients of 55 years or more, who have heart or circulation problems or have previously had a stroke, Ramipril Tablets may help to reduce the risk of heart attack, stroke and further heart and circulation problems. They can also help to reduce the need for surgical procedures to improve the circulation such as a heart bypass operation. You may also be given Ramipril Tablets if you are a diabetic of 55 years or more who smokes and have suffered from heart and circulation problems, high blood pressure, high cholesterol or protein in your urine.

2. BEFORE YOU TAKE RAMIPRIL TABLETS

Do not take Ramipril Tablets:
- If you are hypersensitive (allergic) to ramipril or any of the other ingredients in Ramipril Tablets;
- If you are pregnant or breastfeeding;
- If you have previously suffered a condition called angioneurotic oedema (swelling particularly of the hands, feet, face, tongue and throat with no apparent cause);
- If you have low or rapidly changing blood pressure;
- If you have had problems with the blood supply to your kidneys.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before talking this medicinal product.

It is important to talk to your doctor before you take Ramipril Tablets if you have any of the following conditions:

- A narrowing of heart valves or blockage;
- Kidney problems;
- Liver disease;
- You are on haemodialysis or any other type of blood filtration. If you are on haemodialysis using high flux polyacrylonitrile (AN69) membranes, inform your doctor so that a different technique can be chosen to prevent hypersensitivity reactions.
- Collagen vascular disease such as lupus or scleroderma;
- Problems with salt imbalances such as high sodium or low potassium. These may be caused by dehydration through vomiting or diarrhoea or in people on a low salt diet.

If you need to have an operation or an anaesthetic, tell your doctor or dentist that you are taking Ramipril Tablets.

Pregnancy
Ask your doctor or pharmacist for advice before taking any medicine.
Ramipril Tablets should not be taken if you are pregnant or think you may be pregnant, as Ramipril Tablets may harm the unborn baby.

Breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.
Ramipril Tablets should not be taken by women who are breastfeeding.

Driving and using machines:
It is not advisable to drive or operate machinery for several hours after the first dose of Ramipril Tablets or after an increase in dose.
You should not drive or operate machinery if you feel dizzy or tired while taking Ramipril Tablets.

Drinking alcohol may make the dizziness or sleepiness worse.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. In particular, you should inform your doctor if you have taken or have recently taken any of the following medicines:

- Diuretics (water tablets)
- Medicines for high blood pressure or heart disease such as beta blockers (propranolol or atenolol), calcium channel blockers (nifedipine or diltiazem) or alpha blockers (doxazosin)
- Medicines for diabetes
- Lithium
- Medicines for treatment of gout such as allopurinol
- Non steroidal anti-inflammatory drugs (NSAID's) such as aspirin or ibuprofen
- Corticosteroids such as hydrocortisone
- Immunosuppressants such as ciclosporin
- Potassium salts

3. HOW TO TAKE RAMIPRIL TABLETS

Always take Ramipril Tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. Exactly how many tablets, and how often you must take them, will be written on the label. Please read it carefully. The recommended doses are given below. However, doctors sometimes prescribe different doses to these: if this applies to you, discuss it with your doctor, if you have not already done so.

Swallow the tablet whole with a glass of water. Take the dose at approximately the same time each day.

High blood pressure and congestive heart failure: the usual starting dose is 1.25 mg once a day. Your doctor may decide to increase the dose after 1 -2 weeks. Most people need doses of 2.5 mg or 5 mg once a day, but your doctor may decide you need a different dose, up to a maximum of 10 mg once a day.
Following a heart attack: the usual starting dose is 2.5 mg twice a day which may be increased to 5 mg twice a day after a few days. In some cases the dose may be reduced to 1.25 mg twice a day.
Reducing the risk of heart attack, stroke and the need for surgery to improve blood flow to your heart: the usual starting dose is 2.5 mg once a day. This dose will gradually be increased by your doctor. After three weeks of treatment the dose is usually 10 mg once a day.

If you are elderly and are taking water tablets or have heart, kidney or liver problems your doctor may start your treatment on a lower dose and increase it if needed.

If you forget to take Ramipril Tablets

If you forget to take a dose, take it as soon as you remember, then go on as before. Do NOT take two doses within about 2 hours of each other.

If you take more Ramipril Tablets than you should:

If you accidentally take too many tablets you should contact your doctor or nearest hospital casualty department immediately.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ramipril Tablets can have side effects. The most common of these effects include nausea, dizziness and headache. Other possible, but less common, side effects are described below.

Blood circulation: low blood pressure with dizziness, weakness and nausea. Fainting. Rare reports of chest pain, fast or changing heart beat, syncope, angina, heart attack or stroke, chest pains, palpitations and rhythm disturbances.

Kidney problems: in some people ramipril may affect the kidneys. Pre-existing proteinurea (elevated protein levels in the urine) may deteriorate.

Gastrointestinal: dry mouth, irritation or swelling in the mouth, stomach pains, diarrhoea or constipation, feeling or being sick, changes in liver enzymes (including Jaundice), other forms of impaired liver function, hepatitis and (gastritis-like) stomach pains. Rare reports of pancreatitis (inflammation of the pancreas).

Allergic reactions: pruritis, itchy skin, rash, shortness of breath and sometimes fever.

Skin: reddening of skin areas with accompanying heat sensation, conjunctivitis (eye infection), itching, urticaria, other skin or mucosal eruptions, pronounced hair loss and reduced circulation to the hands and/or feet (Raynaud's phenomenon). As with other medicines of this type (i.e. ACE inhibitors) psoriasiform and pemphigoid exanthema and enanthema, sensitivity of the skin to light and effects on the nails (loosening) have been observed.

Respiratory tract: dry tickling cough, bronchitis, sinusitis, rhinitis, bronchospasm and a runny or stuffy nose.

Angioneurotic oedema: in very rare cases this condition has occurred which includes symptoms such as swelling of the face, tongue and throat.

Other effects: disturbance of balance, headache, nervousness, restlessness, tremor, problems with sleeping, confusion, loss of appetite, depressed mood, feeling of anxiety, raised antinuclear antibodies, pins and needles, muscle cramps, muscle and joint pains, fever, vasculitis (inflammation of the blood vessels), sexual inability in men, and reduced sexual desire (libido). A very small number of people find that this medicine affects their sense of taste.

Blood tests may show an increase in some liver test results. An increase in blood urea nitrogen, creatinine levels, serum potassium levels and a decrease in serum sodium levels may also be observed. Taking Ramipril may result in an increase in the number of so-called eosinophilic blood cells.

Tell your doctor at once if:

- You feel ill after your first dose (a few people may react to their first dose and feel very dizzy, weak, faint and sick);
- You get a lot of infections with sore throats or mouth ulcers;
- You notice a rash, skin eruption or other effects on your skin or eyes, itching or a high temperature;
- You notice swelling of the face, tongue or throat.

Ask your doctor if you should continue taking the tablets.

Stop taking Ramipril Tablets immediately and go to your doctor or casualty department if:

- Your breathing becomes difficult and noisy;
- You get any swelling of the face, tongue or throat.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING RAMIPRIL TABLETS

Do not take this medicine after the expiry date stated on the carton. Any out of date medicines should be returned to your pharmacist for safe disposal. If you notice any visible signs of deterioration in the tablets, take them to your pharmacist for advice before taking them.
Do not store above 25°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

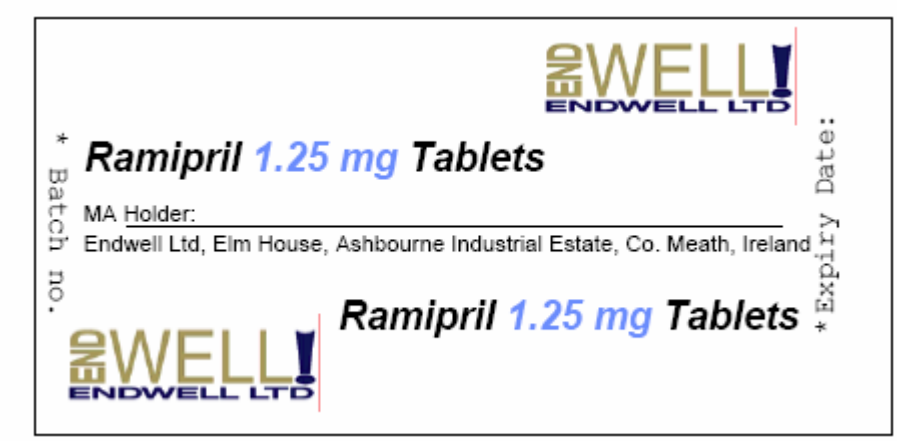
REMEMBER this medicine is for you. Only a doctor can prescribe it for you. Never give it to others. It may harm them, even if their symptoms are the same as yours.

Date of preparation of leaflet March 2006

RAMIPRIL TABLETS (RAMIPRIL)
PL 18843/0014-17

LABELLING

BLISTER



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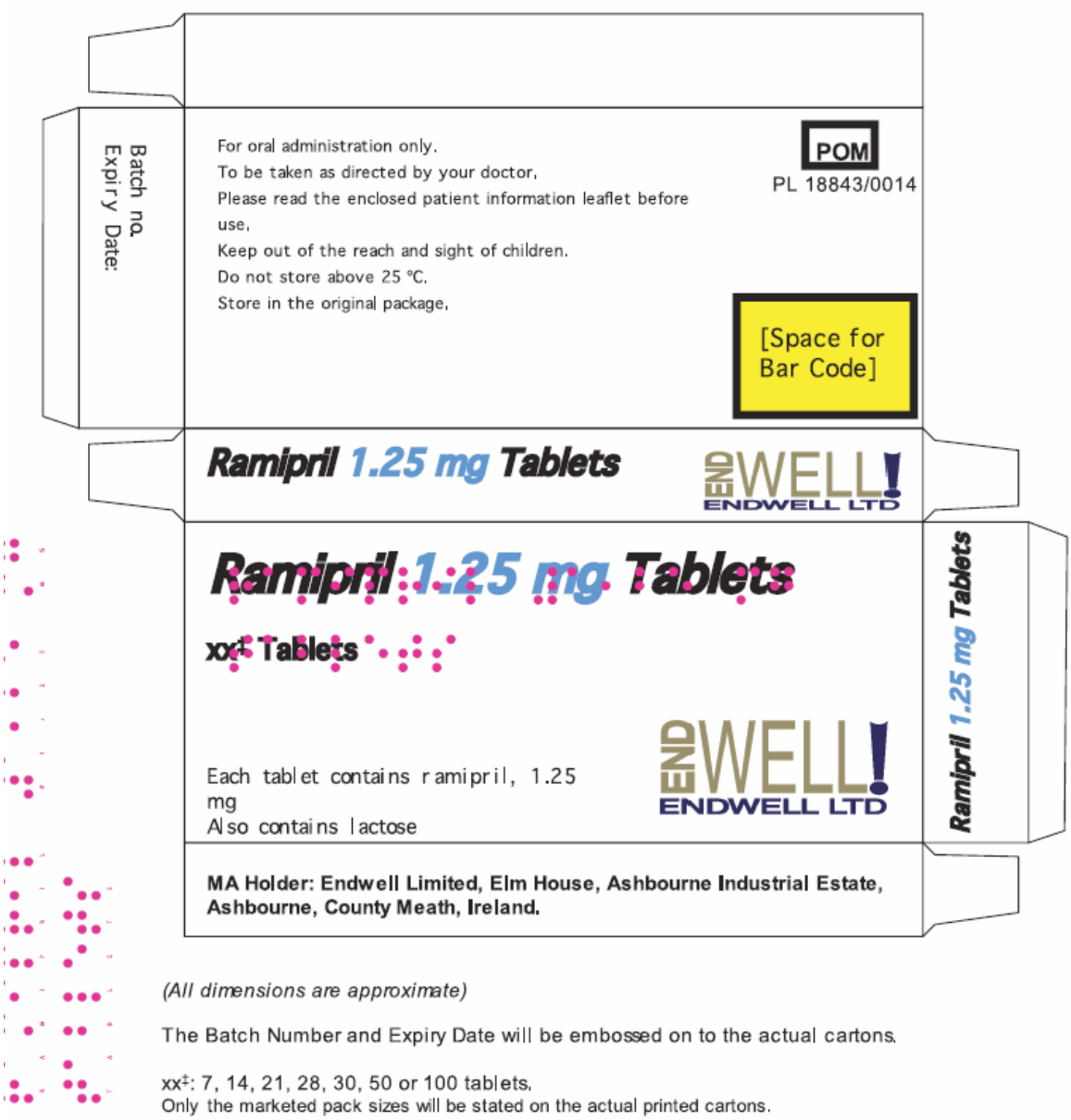

(All dimensions are approximate)

The Batch Number and Expiry Date will be embossed on to the actual cartons.

xx‡: 7, 14, 21, 28, 30, 50 or 100 tablets.
Only the marketed pack sizes will be stated on the actual printed cartons.