The European Agency for the Evaluation of Medicinal Products

London, 4 December 2003
CPMP/3175/03

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

SUMMARY INFORMATION ON REFERRAL OPINION

PURSUANT TO ARTICLE 30 OF COUNCIL DIRECTIVE 2001/83/EC FOR

Renitec and associated names (See Annex I)

International Non-Proprietary Name (INN): enalapril

BACKGROUND INFORMATION

Enalapril is a highly specific, competitive inhibitor of Angiotensin-I Converting Enzyme (ACE), belonging to the category of ACE inhibitors. The beneficial effects of ACE inhibitors appear to result primarily from the suppression of the plasma renin-angiotensin-aldosterone system.

From the authorisations in Member States, different Summaries of Product Characteristics (SPC) had been issued, based on national, divergent decisions. On 31 October 2000, France presented to the EMEA a referral under Article 30 of Directive 2001/83/EC[1].

The referral procedure started on 31 May 2001 in order to harmonise the Summaries of Product Characteristics within the Member States, Norway and Iceland. The CPMP having considered the Rapporteur and the Co-Rapporteur assessment reports, the scientific discussion within the Committee and the comments from the Marketing Authorisation Holders (MAH) during the Oral Explanation on 18 September 2002, was of the opinion that the benefit/risk ratio of enalapril is considered to be favourable for use related to hypertension, symptomatic heart failure and prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction (ejection fraction ≤35%). The CPMP issued a positive opinion, on 19 September 2002, recommending the harmonisation of the SPC for Renitec and associated names.

The CPMP Opinion dated 19 September 2002 was appealed by the MAH on 15 November 2002. The MAH was invited to an Oral Explanation at the December CPMP meeting, but notified the EMEA of their wish not to attend this hearing.

After consideration of the grounds for appeal submitted by the MAH in their letter of 15 November 2002 and all available data and the discussion that followed within the Committee, the CPMP, during the meeting of 17 – 18 December 2002 recommended that its Opinion of 19 September 2002 should be revised. The agreed indications for Renitec are: treatment of hypertension, treatment of symptomatic heart failure and prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction (ejection fraction ≤35%).

The list of product names concerned is given in Annex I. An overall summary of the scientific evaluation of Renitec (and associated names) including the scientific conclusion following the appeal are provided in Annex II together with the amended Summary of Product Characteristics in Annex III.

A Decision was issued by the European Commission on 21 May 2003.

[1] Corresponding to Article 11 of Directive 75/319/EEC, for referrals presented before 18 December 2001

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ANNEX I

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

Member State	Marketing Authorisation Holder	Invented name / Name	Strength	Pharmaceutical Form	Route of administration	Packaging	Package-size
Austria	Merck Sharp & Dohme G.m.b.H.	RENITEC 5 mg Tabletten	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	Donau Citystr. 6	RENITEC 10 mg Tabletten	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	A-1220 Wien	RENITEC 20 mg Tabletten	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
	Kwizda	MEPRIL	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	Effingergasse 21	MEPRIL	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	A-1160 Wien	MEPRIL	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
Belgium	Merck Sharp & Dohme BV	RENITEC	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	14 tablets
	Chaussée de waterloo 1135	RENITEC	5 mg	Tablets	Oral use	Blister (Alu/Alu)	14, 28 tablets and 28 x 1 (unit dose)
	1180 Bruxelles - Belgium	RENITEC	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 56 tablets
		RENITEC	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 56, 98 tablets and 28 x 1 (unit dose)
Denmark	Merck Sharp & Dohme B.V.	RENITEC	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	49 tablets
	Waarderweg 39	RENITEC	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
	2031 BN H aarlem, Nederland	RENITEC	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
		RENITEC	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
Finland	Merck Sharp & Dohme B.V.	RENITEC	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	49 tablets
	Waarderweg 39	RENITEC	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
	2031 BN Haarlem, Nederland					Bottle (glass)	100 tablets
		RENITEC	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
						Bottle (glass)	100 tablets
		RENITEC	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
						Bottle (glass)	100 tablets
	Oy Leiras Finland Ab	ENALOC	5 mg	Tablets	Oral use	Bottle (glass)	30, 100 tablets
	Yliopistonkatu 34 A, PO Box 102	ENALOC	10 mg	Tablets	Oral use	Bottle (glass)	30, 100 tablets
	FIN-20101 Turku	ENALOC	20 mg	Tablets	Oral use	Bottle (glass)	30, 100 tablets

France	MSD-Chibret - 3 avenue Hoche	RENITEC cp sécable	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	11 tablets
	75114 Paris cedex 08	RENITEC cp sécable	5 mg	Tablets	Oral use	Blister (Alu/Alu)	14, 28, 50 tablets
		RENITEC cp sécable	20 mg	Tablets	Oral use	Blister (Alu/Alu)	14, 28, 50 tablets
	MSD-Chibret - 3 avenue Hoche	Enalapril MSD 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	14, 28, 50 tablets
	75114 Paris cedex 08	Enalapril MSD 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	14, 28, 50 tablets
		Enalapril Chibret 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	14, 28, 50 tablets
		Enalapril Chibret 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	14, 28, 50 tablets
Germany	MSD SHARP & DOHME GMBH	XANEF Cor 2.5 mg	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
	Lindenplatz 1, 85540 Haar	XANEF 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
		XANEF 10 mg	10 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
		XANEF 20mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
		RACEN Cor 2.5 mg	2,5 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
		RACEN 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
		RACEN 10mg	10 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
		RACEN 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
	Boehringer Ingelheim Pharma KG	PRES 2.5 mg	2,5 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
	Binger Str., 55216 Ingelheim	PRES 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
		PRES 10 mg	10 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
		PRES 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50, 100, 300 tablets
Greece	Vianex S.A, Tatoiou str.,	RENITEC	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	20, 30, 40 tablets
	18th Km Athens-Lamia National Road,	RENITEC	5 mg	Tablets	Oral use	Blister (Alu/Alu)	30 tablets
	14671 N. Erithrea-Greece	RENITEC	20 mg	Tablets	Oral use	Blister (Alu/Alu)	10 tablets
		VITOBEL	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	20, 30, 40 tablets
		VITOBEL	5 mg	Tablets	Oral use	Blister (Alu/Alu)	30 tablets
		VITOBEL	20 mg	Tablets	Oral use	Blister (Alu/Alu)	10 tablets
Ireland	Merck Sharp & Dohme Limited	INNOVACE Tablets 2.5 mg	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	2, 11, 28 tablets
	Hertford Road, Hoddesdon	INNOVACE Tablets 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	2, 14, 28 tablets
	Herts, EN11 9BU, UK	INNOVACE Tablets 10 mg	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
		INNOVACE Tablets 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
		INNOVACE Tablets 40 mg	40 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets

Italy	Merck Sharp & Dohme (Italia) S.p.A.	ENAPREN	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	Via G. Fabbroni, 6 - 00191 Roma	ENAPREN	20 mg	Tablets	Oral use	Blister (Alu/Alu)	14 tablets
	Istituto Gentili S.p.A. Via Mazzini, 112	CONVERTEN	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	56125 Pisa	CONVERTEN	20 mg	Tablets	Oral use	Blister (Alu/Alu)	14 tablets
	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.	NAPRILENE	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	V.le Shakespeare, 47 - 00144 Roma	NAPRILENE	20 mg	Tablets	Oral use	Blister (Alu/Alu)	14 tablets
Luxembourg	Merck Sharp & Dohme BV	RENITEC	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	14 tablets
	Chaussée de waterloo 1135	RENITEC	5 mg	Tablets	Oral use	Blister (Alu/Alu)	14, 28 tablets and 28 x 1 (unit dose)
	1180 Bruxelles - Belgium	RENITEC	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 56 tablets
		RENITEC	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 56, 98 tablets and 28 x 1 (unit dose)
Netherlands	Merck Sharp & Dohme B.V.,	RENITEC 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50 tablets
	P.O. Box 581, 2003 PC Haarlem	RENITEC 10 mg	10 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50 tablets
	Nederland	RENITEC 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50 tablets
		RENITEC 40 mg	40 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 50 tablets
Portugal	Merck Sharp & Dohme, Lda	RENITEC 2.5	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	20, 60 tablets
	Quinta da Fonte 19 Porto Salvo	RENITEC 5	5 mg	Tablets	Oral use	Blister (Alu/Alu)	20, 60 tablets
	2780-730 Paço de Arcos	RENITEC 10	10 mg	Tablets	Oral use	Blister (Alu/Alu)	10, 60 tablets
		RENITEC	20 mg	Tablets	Oral use	Blister (Alu/Alu)	30, 60 tablets
Spain	MERCK SHARP & DOHME DE ESPAÑA, S.A.	RENITEC 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	10, 60 tablets
	Josefa Valcarcel, 38, 28027 Madrid	RENITEC 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 500 tablets
	LABORATORIOS ABELLÓ, S.A.	ENALAPRIL ABELLÓ 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	10, 60 tablets
	Josefa Valcarel, 38, 28027 Madrid	ENALAPRIL ABELLÓ 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	IQUINOSA, Alpedrete, 24,	PRESITAN 5	5 mg	Tablets	Oral use	Blister (Alu/Alu)	10, 60 tablets
	28045 Madrid	PRESITAN 20	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	SIGMA-TAU, S.A. Poligono Industrial Azque,	NAPRILENE 5	5 mg	Tablets	Oral use	Blister (Alu/Alu)	10, 60 tablets

	Bolivia 15, Alcala de Henares 28806 Madrid	NAPRILENE 20	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
	URIACH, Dega Bahi, 59	CRINOREN 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	10, 60 tablets
	08026 Barcelona	CRINOREN 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
Sweden	Merck Sharp & Dohme B.V.	RENITEC	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	49 tablets
	Waarderweg 39	RENITEC	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 49, 98 tablets
	2031 BN Haarlem, Nederland					Bottle (glass)	100 tablets
		RENITEC	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 49, 98 tablets
						Bottle (glass)	100 tablets
		RENITEC	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 49, 98 tablets
						Bottle (glass)	100 tablets
UK	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon	INNOVACE Tablets 2.5 mg	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	2, 11, 28 tablets
	Herts, EN11 9BU, UK	INNOVACE Tablets 5 mg	5 mg	Tablets	Oral use	Blister (Alu/Alu)	2, 14, 28 tablets
		INNOVACE Tablets 10 mg	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets
		INNOVAVE Tablets 20 mg	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28 tablets

Iceland	Merck Sharp & Dohme B.V.	RENITEC	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	49 tablets
	Waarderweg 39	RENITEC	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
	2031 BN Haarlem, Nederland	RENITEC	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
		RENITEC	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 98 tablets
Norway	Merck Sharp & Dohme B.V.	RENITEC	2.5 mg	Tablets	Oral use	Blister (Alu/Alu)	11, 49 tablets
	Waarderweg 39	RENITEC	5 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 49, 98 tablets
	2031 BN Haarlem, Nederland	RENITEC	10 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 49, 98 tablets
		RENITEC	20 mg	Tablets	Oral use	Blister (Alu/Alu)	28, 49, 98 tablets
		RENITEC	2.5 mg + 10 mg	Tablets	Oral use	Blister (Alu/Alu)	11 x (2.5 mg) + 14 x (10 mg) tablets

ANNEX II

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

SCIENTIFIC CONCLUSIONS

Overall Summary of the Scientific Evaluation of Renitec and associated names

- Quality issues

No significant issues relating to Quality were identified.

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

- Efficacy issues

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

Section 4.1 Therapeutic Indications

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

- hypertension, especially renovascular hypertension;
- heart failure, especially as regards associated claims of reduction of morbidity and mortality and the use of Renitec as adjunctive therapy to diuretics and digitalis;
- the use of Renitec for prevention of coronary ischaemic events.

After an assessment of all available data, the documentation provided by the MAH in support of the Oral Explanation on 18 September 2002, the discussion that took place between the MAH and the CPMP, an evaluation of the current EU-wide clinical practices relating to the use of Renitec, it was the opinion of the CPMP that the following wordings of the indications for Renitec are scientifically substantiated, adequately worded and in accordance with the CPMP Guideline on Summary of Product Characteristics. The following was considered by the Committee to be the most suitable harmonised Section 4.1 indications text:

4.1 Therapeutic indications

- Hypertension
- Symptomatic Heart Failure
- Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤35%)

(see section 5.1 Pharmacodynamic properties)

Section 4.2 Posology and method of administration

After an assessment of the documentation provided by the MAH to substantiate scientifically the divergent information across Member States and justify a proposed common wording, especially with regard to the recommended starting dose in hypertension, and the recommendations on dosage in renal insufficiency and paediatric use, and following an evaluation of the current EU-wide clinical practices relating to the use of Renitec, the wording considered to be the most suitable harmonised Section 4.2 Posology text was agreed with the applicant (see Annex III).

- Safety issues

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

Section 4.3 Contraindications

The MAH was requested to propose and scientifically justify a common EU wide approach, as there were significant differences between Member States in particular regarding:

- use of Renitec in pregnancy
- use of Renitec in children
- use of Renitec in severe renal impairment, after renal transplantation, in liver disease, in aortic or mitral valve stenosis.

After an assessment of the documentation provided by the MAH and an evaluation of the current EU-wide clinical practices relating to the use of Renitec, the following was considered to be the most suitable harmonised Section 4.3 Contraindications text:

4.3 Contraindications

- Hypersensitivity to enalapril, to any of the excipients or any other ACE inhibitor
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see 4.6 Pregnancy and lactation).

Section 4.4. Special warnings and precautions for use

After assessment of the documentation provided by the MAH to substantiate scientifically the divergent information across Member States and justify a proposed common wording and following an evaluation of the current EU-wide clinical practices relating to the use of Renitec, the most suitable harmonised Section 4.4 Special Warnings and Precautions for Use text was approved (see Annex III).

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

- Administrative issues

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

Benefit/Risk considerations

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CPMP considered that the benefit/risk ratio of Renitec is favourable for use relating to hypertension, symptomatic heart failure and asymptomatic left ventricular dysfunction (ejection fraction $\leq$35%).

Scientific Conclusion of the Appeal

The CPMP Opinion dated 19 September 2002 was appealed by the MAH on 15 November 2002. In their letter of 15 November 2002 the MAH presented the Grounds for Appeal against the Opinion of 19 September 2002 (see Appendix 2 of the CPMP Opinion of 18 December 2002) in accordance with article 32(4) of Directive 2001/83/EC. The MAH was invited to an Oral Explanation at the December CPMP meeting, but notified the EMEA of their wish not to attend this hearing. The MAH took the view that the Opinion of 19 September 2002 should be revised and the indication section of the SPC should read as follows:

4.1 Therapeutic indications

- Hypertension

- Symptomatic Heart Failure;
  to reduce mortality and morbidity, including to reduce hospitalization for Heart Failure and to slow progression of Heart Failure.

- Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤35%) to prevent the Development of Symptomatic Heart Failure.

(see section 5.1 Pharmacodynamic properties)

The MAH considered that section 4.1 should include information concerning the specific treatment objectives/outcomes with regard to symptomatic heart failure (see underlined text above). Such specific treatment outcomes in section 4.1 of the SPC were previously approved in several EU Member States. The MAH disagreed with the CPMP final assessment report as appended to the CPMP Opinion of 19 September 2002. The MAH, however, agreed with the wording of the indications hypertension and prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction.

After consideration of the Grounds for Appeal as submitted by the MAH in their letter dated 15 November 2002 and the discussion that followed within the Committee, the CPMP reached the following conclusions:

The referral was presented to the EMEA by France under Article 30 of Directive 2001/83/EEC, with the clearly identified question to harmonise the national SPCs of their medicinal product Renitec and associated names with reference to in particular the sections on indications, posology and contraindications. During the referral procedure, no clinically or scientifically relevant information has been removed from the SPC. As part of the harmonisation process, some information has been repositioned, for instance from section 4.1 to section 5.1.
Such a harmonisation procedure is in the interest of the patient since a uniform SPC will result in a more uniform Patient Leaflet (PL) within the EU. The objective of the harmonisation exercise is to agree on an overall uniform SPC and it is therefore not possible to restrict the discussion to certain parts of the SPC text. During this exercise it was not the intention of the CPMP to delete any relevant information from the SPC and the MAH did not object to any proposals to delete less relevant information. In line with the discussion above, however, there was a need to move information on clinical outcome to other more relevant parts of the SPC. In addition, for other anti-hypertensive medicinal products, treatment objectives are not mentioned in section 4.1 of the SPC.

The CPMP and the MAH share the view that the indication symptomatic heart failure is sufficiently substantiated from a scientific point of view given the outcome of the SOLVD study, all in line with the requirements of the guideline for investigation of heart failure. However, the MAH disagreed with the CPMP assessment report stating that the proven benefits of Renitec are common to the class of ACE inhibitors, even though specific products may have been documented in somewhat different populations and circumstances. However, the indication in heart failure has only been authorised for those ACE-inhibitors that have indeed shown therapeutic benefit in clinical trials. Detailed evidence-based information and claims of gains in morbidity/mortality with Renitec (enalapril) over other ACE inhibitors in the treatment of heart failure, reflecting the outcome of the clinical studies performed, should be described in section 5.1 of the SPC together with a clear definition of the target population(s). The CPMP does not believe that moving outcome claims from section 4.1 to section 5.1 would undermine the value of conducting large outcome clinical trials to demonstrate additional benefits associated with a medicinal product as suggested by the MAH.

Further, the MAH argued that patients would suffer from the relocation of outcome data from section 4.1 to section 5.1. The view was that the deletion of this information from the PL might give the false impression that the benefits of enalapril no longer exist and as a result this might undermine the confidence in the prescribed medication. The CPMP does not share the view of the MAH since the indication as such has not been deleted.

In the view of the CPMP, the MAH has not given sufficient arguments in favour of accepting the Grounds for Appeal. There are therefore no reasons for major change to the original opinion for Renitec (enalapril) adopted on 19 September 2002. However, during the discussions within the CPMP, it was clear that a minor amendment should be made to the original wording agreed during the Renitec (enalapril) referral, to add the word "treatment" to the target disease/ target population in order to include the element of treatment objective. It was therefore decided that section 4.1 should be revised slightly to include the wording "Treatment of Symptomatic Heart Failure" and "Treatment of Hypertension" and the CPMP Opinion of 19 September 2002 should be revised accordingly.

In conclusion, after consideration of the grounds for appeal as submitted by the MAH in their letter of 15 November 2002 and the discussion that followed within the Committee, it is the Opinion of the CPMP that the recommended wordings of the indications for Renitec are scientifically substantiated and in accordance with the CPMP Guideline on Summary of Product Characteristics. The omission of therapy objectives/outcomes from the indication text and the positioning of this information in section 5.1 of the SPC would not detract from the information value to the prescriber. The adopted therapeutic indication text for Renitec (enalapril) thus reads:

4.1 Therapeutic indications

- Treatment of Hypertension.
- Treatment of Symptomatic Heart Failure.
- Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤35%).

(see section 5.1 Pharmacodynamic properties)

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics,
- the Summary of Products Characteristics proposed by the Marketing Authorisation Holders was assessed based on the documentation submitted, the information provided by the MAH at an oral explanation on 18 September 2002 and the scientific discussion within the Committee,
- the CPMP adopted its Opinion on 19 September 2002,
- the MAH appealed the CPMP Opinion of 19 September 2002,
- the CPMP having assessed the grounds for appeal submitted by the MAH on 15 November 2002,

the CPMP recommends that its Opinion of 19 September 2002 should be revised to take into account the changes detailed above in accordance with the revised Summary of Product Characteristics (see Annex III).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note:
This SPC is the one that was annexed to the Commission Decision concerning this referral; the text was valid at that time. It is not subsequently maintained or updated by the EMEA, and therefore may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<Renitec and associated names (see Annex I)>, <strength>, tablets.
[To be implemented nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains <strength> mg enalapril maleate.
[To be implemented nationally]

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of Hypertension.
- Treatment of Symptomatic Heart Failure.
- Prevention of Symptomatic Heart Failure in patients with Asymptomatic Left Ventricular Dysfunction (ejection fraction ≤35%).

(See Section 5.1 Pharmacodynamic properties.)

4.2 Posology and method of administration

The absorption of <Renitec> is not affected by food.

The dose should be individualized according to patient profile (see 4.4 Special warnings and special precautions for use) and blood pressure response.

Hypertension
The initial dose is 5 to maximally 20 mg, depending on the degree of hypertension and the condition of the patient (see below). <Renitec> is given once daily. In mild hypertension, the recommended initial dose is 5 to 10 mg. Patients with a strongly activated renin-angiotensin-aldosterone system (e.g., renovascular hypertension, salt and/or volume depletion, cardiac decompensation, or severe hypertension) may experience an excessive blood pressure fall following the initial dose. A starting dose of 5 mg or lower is recommended in such patients and the initiation of treatment should take place under medical supervision.

Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril. A starting dose of 5 mg or lower is recommended in such patients. If possible, diuretic therapy should be discontinued for 2-3 days prior to initiation of therapy with <Renitec>. Renal function and serum potassium should be monitored.

The usual maintenance dose is 20 mg daily. The maximum maintenance dose is 40 mg daily.

Heart Failure/Asymptomatic Left Ventricular Dysfunction

In the management of symptomatic heart failure, <Renitec> is used in addition to diuretics and, where appropriate, digitalis or beta-blockers. The initial dose of <Renitec> in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction is 2.5 mg, and it should be administered under close medical supervision to determine the initial effect on the blood pressure. In the absence of, or after effective management of, symptomatic hypotension following initiation of therapy with <Renitec> in heart failure, the dose should be increased gradually to the usual maintenance dose of 20 mg, given in a single dose or two divided doses, as tolerated by the patient. This dose titration is recommended to be performed over a 2 to 4 week period. The maximum dose is 40 mg daily given in two divided doses.

Suggested Dosage Titration of <Renitec>in Patients with Heart Failure/Asymptomatic Left Ventricular Dysfunction

Week	**Dose mg/day**
Week 1	**Days 1 to 3:** 2.5 mg/day* in a single dose **Days 4 to 7:** 5 mg/day in two divided doses
Week 2	10 mg/day in a single dose or in two divided doses
Weeks 3 and 4	20 mg/day in a single dose or in two divided doses

*Special precautions should be followed in patients with impaired renal function or taking diuretics (See 4.4 Special warnings and special precautions for use).

Blood pressure and renal function should be monitored closely both before and after starting treatment with <Renitec> (see 4.4 Special warnings and special precautions for use) because hypotension and (more rarely) consequent renal failure have been reported. In patients treated with diuretics, the dose should be reduced if possible before beginning treatment with<Renitec>. The appearance of hypotension after the initial dose of <Renitec> does not imply that hypotension will recur during chronic therapy with <Renitec>and does not preclude continued use of the drug. Serum potassium and renal function also should be monitored.

Dosage in Renal Insufficiency

Generally, the intervals between the administration of enalapril should be prolonged and/or the dosage reduced.

Creatinine Clearance (CrCL) mL/min	**Initial Dose mg/day**
30<CrCL<80 ml/min.	5 - 10 mg
10<CrCL≤30 ml/min.	2.5 mg
CrCL≤10 ml/min.	2.5 mg on dialysis days*

* See 4.4 Special warnings and special precautions for use - Hemodialysis Patients. Enalaprilat is dialyzable. Dosage on nondialysis days should be adjusted depending on the blood pressure response.

Use in Elderly
The dose should be in line with the renal function of the elderly patient (see 4.4 Special warnings and special precautions for use, Renal Function Impairment).

Use in paediatrics
There is limited clinical trial experience of the use of <Renitec> in hypertensive paediatric patients (see 4.4 Special warnings and special precautions for use, 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties).

For patients who can swallow tablets, the dose should be individualized according to patient profile and blood pressure response. The recommended initial dose is 2.5 mg in patients 20 to <50 kg and 5 mg in patients ≥50 kg. <Renitec> is given once daily. The dosage should be adjusted according to the needs of the patient to a maximum of 20 mg daily in patients 20 to <50 kg and 40 mg in patients ≥50 kg. (See 4.4 Special warnings and special precautions for use.)

<Renitec> is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2, as no data are available.

4.3 Contraindications

- Hypersensitivity to enalapril, to any of the excipients or any other ACE inhibitor
- History of angioedema associated with previous ACE inhibitor therapy
- Hereditary or idiopathic angioedema
- Second and third trimesters of pregnancy (see 4.6 Pregnancy and lactation).

4.4 Special warnings and special precautions for use

Symptomatic Hypotension
Symptomatic hypotension is rarely seen in uncomplicated hypertensive patients. In hypertensive patients receiving <Renitec>, symptomatic hypotension is more likely to occur if the patient has been volume - depleted, e.g., by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting (see 4.5 Interaction with other medicaments and other forms of interaction and 4.8 Side Effects). In patients with heart failure, with or without associated renal insufficiency, symptomatic hypotension has been observed. This is most likely to occur in those patients with more severe degrees of heart failure, as reflected by the use of high doses of loop diuretics, hyponatremia or functional renal impairment. In these patients, therapy should be started under medical supervision and the patients should be followed closely whenever the dose of <Renitec> and/or diuretic is adjusted. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

In some patients with heart failure who have normal or low blood pressure, additional lowering of systemic blood pressure may occur with <Renitec>. This effect is anticipated, and usually is not a reason to discontinue treatment. If hypotension becomes symptomatic, a reduction of dose and/or discontinuation of the diuretic and/or <Renitec> may be necessary.

Aortic or Mitral Valve Stenosis/Hypertrophic Cardiomyopathy
As with all vasodilators, ACE inhibitors should be given with caution in patients with left ventricular valvular and outflow tract obstruction and avoided in cases of cardiogenic shock and haemodynamically significant obstruction.

Renal Function Impairment
In cases of renal impairment (creatinine clearance <80 ml/min) the initial enalapril dosage should be adjusted according to the patient's creatinine clearance (see 4.2 Posology and method of administration) and then as a function of the patient's response to treatment. Routine monitoring of potassium and creatinine are part of normal medical practice for these patients.

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

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea and creatinine when enalapril has been given concurrently with a diuretic. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. This situation should raise the possibility of underlying renal artery stenosis (see 4.4 Special warnings and special precautions for use, Renovascular hypertension).

Renovascular hypertension
There is an increased risk of hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with ACE inhibitors. Loss of renal function may occur with only mild changes in serum creatinine. In these patients, therapy should be initiated under close medical supervision with low doses, careful titration, and monitoring of renal function.

Kidney Transplantation
There is no experience regarding the administration of <Renitec> in patients with a recent kidney transplantation. Treatment with <Renitec> is therefore not recommended.

Hepatic failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

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

Hypersensitivity/Angioneurotic Edema
Angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including <Renitec>. This may occur at any time during treatment. In such cases, <Renitec> should be discontinued promptly and appropriate monitoring should be instituted to ensure complete resolution of symptoms prior to dismissing the patient. In those instances where swelling has been confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioneurotic edema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, which may include subcutaneous epinephrine solution 1:1000 (0.3 ml to 0.5 ml) and/or measures to ensure a patent airway, should be administered promptly.

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks.

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

Anaphylactoid Reactions during Hymenoptera Desensitization
Rarely, patients receiving ACE inhibitors during desensitization with hymenoptera venom have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each desensitization.

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

Hemodialysis Patients
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Diabetic patients
In diabetic patients treated with oral antidiabetic agents or insulin, glycemic control should be closely monitored during the first month of treatment with an ACE inhibitor. (See 4.5 Interaction with other medicinal products and other forms of interaction, Antidiabetics.)

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril blocks angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

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

Lithium
The combination of lithium and enalapril is generally not recommended (see 4.5 Interaction with other medicinal products and other forms of interaction).

Lactose
<Renitec> contains less than 200 mg of lactose per tablet.

Paediatric Use
There is limited efficacy and safety experience in hypertensive children >6 years old, but no experience in other indications. Limited pharmacokinetic data are available in children above 2 months of age. (Also see 4.2 Posology and method of administration, 5.1 Pharmacodynamic properties, and 5.2 Pharmacokinetic properties.) <Renitec> is not recommended in children in other indications than hypertension.

<Renitec> is not recommended in neonates and in paediatric patients with glomerular filtration rate <30 ml/min/1.73 m^2, as no data are available. (See 4.2 Posology and method of administration.)

Pregnancy and lactation
Enalapril should not be used during the first trimester of pregnancy. <Renitec> is contraindicated in the second and third trimesters of pregnancy (see 4.3 Contraindications). When pregnancy is detected, enalapril treatment should be discontinued as soon as possible (see 4.6 Pregnancy and lactation).

Use of enalapril is not recommended during breast feeding.

Ethnic differences
As with other angiotensin converting enzyme inhibitors, enalapril is apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction

Potassium sparing diuretics or potassium supplements
ACE inhibitors attenuate diuretic induced potassium loss. Potassium sparing diuretics (e.g. spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. If concomitant use is indicated because of demonstrated hypokalemia they should be used with caution and with frequent monitoring of serum potassium (see 4.4 Special warnings and special precautions for use).

Diuretics (thiazide or loop diuretics)
Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with enalapril (see 4.4 Special warnings and special precautions for use). The hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake or by initiating therapy with a low dose of enalapril.

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

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

Tricyclic antidepressants/Antipsychotics/Anesthetics/Narcotics
Concomitant use of certain anesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see 4.4 Special warnings and special precautions for use).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Chronic administration of NSAIDs may reduce the antihypertensive effect of an ACE inhibitor.

NSAIDs and ACE inhibitors exert an additive effect on the increase in serum potassium, and may result in a deterioration of renal function. These effects are usually reversible. Rarely, acute renal failure may occur, especially in patients with compromised renal function such as the elderly or dehydrated.

Sympathomimetics
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Antidiabetics
Epidemiological studies have suggested that concomitant administration of ACE inhibitors and antidiabetic medicines (insulins, oral hypoglycemic agents) may cause an increased blood-glucose-lowering effect with risk of hypoglycemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Alcohol
Alcohol enhances the hypotensive effect of ACE inhibitors.

Acetyl salicylic acid, thrombolytics and β-blockers
Enalapril can be safely administered concomitantly with acetyl salicylic acid (at cardiologic doses), thrombolytics and β-blockers.

4.6 Pregnancy and lactation

Pregnancy
Enalapril should not be used during the first trimester of pregnancy. When a pregnancy is planned or confirmed the switch to an alternative treatment should be initiated as soon as possible. Controlled studies with ACE inhibitors have not been done in humans, but a limited number of cases with first trimester exposure have not appeared to manifest malformations consistent with human fetotoxicity as described below.

Enalapril is contraindicated during the second and third trimesters of pregnancy.

Prolonged enalapril exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia). (Also see 5.3 Preclinical safety data.)

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

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

Lactation
Enalapril and enalaprilat are excreted in breast milk but their effect on the nursing infant has not been determined. Consequently, use of enalapril is not recommended if breast-feeding.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

Undesirable effects reported for enalapril include:

Blood and the lymphatic system disorders:
uncommon: anemia (including aplastic and hemolytic)
rare: neutropenia, decreases in hemoglobin, decreases in hematocrit, thrombocytopenia, agranulocytosis, bone marrow depression, pancytopenia, lymphadenopathy, autoimmune diseases

Metabolism and nutrition disorders:
uncommon: hypoglycemia (see 4.4 Special warnings and special precautions for use, Diabetic patients)

Nervous system and psychiatric disorders:
common: headache, depression
uncommon: confusion, somnolence, insomnia, nervousness, paresthesia, vertigo
rare: dream abnormality, sleep disorders

Eye disorders:
very common: blurred vision

Cardiac and vascular disorders:
very common: dizziness
common: hypotension (including orthostatic hypotension), syncope, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see 4.4 Special warnings and special precautions for use), chest pain, rhythm disturbances, angina pectoris, tachycardia
uncommon: orthostatic hypotension, palpitations
rare: Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:
very common: cough
common: dyspnea
uncommon: rhinorrhea, sore throat and hoarseness, bronchospasm/asthma
rare: pulmonary infiltrates, rhinitis, allergic alveolitis/eosinophilic pneumonia

Gastrointestinal disorders:
very common: nausea,
common: diarrhea, abdominal pain, taste alteration
uncommon: ileus, pancreatitis, vomiting, dyspepsia, constipation, anorexia, gastric irritations, dry mouth, peptic ulcer
rare: stomatitis/aphthous ulcerations, glossitis

Hepatobiliary disorders:
rare: hepatic failure, hepatitis – either hepatocellular or cholestatic, hepatitis including necrosis, cholestasis (including jaundice)

Skin and subcutaneous tissue disorders:
common: rash, hypersensitivity/angioneurotic edema: angioneurotic edema of the face, extremities, lips, tongue, glottis and/or larynx has been reported (see 4.4 Special warnings and special precautions for use)
uncommon: diaphoresis, pruritus, urticaria, alopecia
rare: erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, pemphigus, erythroderma

A symptom complex has been reported which may include some or all of the following: fever, serositis, vasculitis, myalgia/myositis, arthralgia/arthritis, a positive ANA, elevated ESR, eosinophilia, and leukocytosis. Rash, photosensitivity or other dermatologic manifestations may occur.

Renal and urinary disorders:
uncommon: renal dysfunction, renal failure, proteinuria
rare: oliguria

Reproductive system and breast disorders:
uncommon: impotence
rare: gynecomastia

General disorders and administration site conditions:
very common: asthenia
common: fatigue
uncommon: muscle cramps, flushing, tinnitus, malaise, fever

Investigations:
common: hyperkalemia, increases in serum creatinine
uncommon: increases in blood urea, hyponatremia
rare: elevations of liver enzymes, elevations of serum bilirubin

4.9 Overdose

Limited data are available for overdosage in humans. The most prominent features of overdosage reported to date are marked hypotension, beginning some six hours after ingestion of tablets, concomitant with blockade of the renin-angiotensin system, and stupor. Symptoms associated with overdosage of ACE inhibitors may include circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough. Serum enalaprilat levels 100- and 200-fold higher than usually seen after therapeutic doses have been reported after ingestion of 300 mg and 440 mg of enalapril, respectively.

The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. If ingestion is recent, take measures aimed at eliminating enalapril maleate (e.g., emesis, gastric lavage, administration of absorbents, and sodium sulphate). Enalaprilat may be removed from the general circulation by hemodialysis. (See 4.4 Special warnings and special precautions for use, Hemodialysis Patients.) Pacemaker therapy is indicated for therapy-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin converting enzyme inhibitors, ATC Code: C09A A02

<Renitec>(enalapril maleate) is the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline. Angiotensin converting enzyme (ACE) is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to the pressor substance angiotensin II. After absorption, enalapril is hydrolyzed to enalaprilat, which inhibits ACE. Inhibition of ACE results in decreased plasma angiotensin II, which leads to increased plasma renin activity (due to removal of negative feedback of renin release), and decreased aldosterone secretion.

ACE is identical to kininase II. Thus <Renitec>may also block the degradation of bradykinin, a potent vasodepressor peptide. However, the role that this plays in the therapeutic effects of <Renitec>remains to be elucidated.

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

Administration of <Renitec>to patients with hypertension results in a reduction of both supine and standing blood pressure without a significant increase in heart rate.

Symptomatic postural hypotension is infrequent. In some patients the development of optimal blood pressure reduction may require several weeks of therapy. Abrupt withdrawal of <Renitec>has not been associated with rapid increase in blood pressure.

Effective inhibition of ACE activity usually occurs 2 to 4 hours after oral administration of an individual dose of enalapril. Onset of antihypertensive activity was usually seen at one hour, with peak reduction of blood pressure achieved by 4 to 6 hours after administration. The duration of effect is dose-related. However, at recommended doses, antihypertensive and hemodynamic effects have been shown to be maintained for at least 24 hours.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with an increase in cardiac output and little or no change in heart rate. Following administration of <Renitec>there was an increase in renal blood flow; glomerular filtration rate was unchanged. There was no evidence of sodium or water retention. However, in patients with low pretreatment glomerular filtration rates, the rates were usually increased.

In short term clinical studies in diabetic and nondiabetic patients with renal disease, decreases in albuminuria and urinary excretion of IgG and total urinary protein were seen after the administration of enalapril.

When given together with thiazide-type diuretics, the blood pressure-lowering effects of <Renitec>are at least additive. <Renitec>may reduce or prevent the development of thiazide-induced hypokalemia.

In patients with heart failure on therapy with digitalis and diuretics, treatment with oral or Injection <Renitec>was associated with decreases in peripheral resistance and blood pressure. Cardiac output increased, while heart rate (usually elevated in patients with heart failure) decreased. Pulmonary capillary wedge pressure was also reduced. Exercise tolerance and severity of heart failure, as measured by New York Heart Association criteria, improved. These actions continued during chronic therapy.

In patients with mild to moderate heart failure, enalapril retarded progressive cardiac dilatation/enlargement and failure, as evidenced by reduced left ventricular end diastolic and systolic volumes and improved ejection fraction.

A multicenter, randomised, double-blind, placebo-controlled trial (SOLVD Prevention trial) examined a population with asymptomatic left ventricular dysfunction (LVEF<35%). 4228 patients were randomized to receive either placebo (n=2117) or enalapril (n=2111). In the placebo group, 818 patients had heart failure or died (38.6%) as compared with 630 in the enalapril group (29.8%) (risk reduction: 29%; 95% CI; 21 - 36%; p<0.001). 518 patients in the placebo group (24.5%) and 434 in the enalapril group (20.6%) died or were hospitalized for new or worsening heart failure (risk reduction 20%; 95% CI; 9 - 30%; p<0.001).

A multicenter, randomised, double-blind, placebo-controlled trial (SOLVD Treatment trial) examined a population with symptomatic congestive heart failure due to systolic dysfunction (ejection fraction <35%). 2569 patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo (n=1284) or enalapril (n=1285). There were 510 deaths in the placebo group (39.7%) as compared with 452 in the enalapril group (35.2%) (reduction in risk, 16%; 95% CI, 5 - 26%; p=0.0036). There were 461 cardiovascular deaths in the placebo group as compared with 399 in the enalapril group (risk reduction 18%, 95% CI, 6 - 28%, p<0.002), mainly due to a decrease of deaths due to progressive heart failure (251 in the placebo group vs 209 in the enalapril group, risk reduction 22%, 95% CI, 6 - 35%). Fewer patients died or were hospitalized for worsening heart failure (736 in the placebo group and 613 in the enalapril group; risk reduction, 26%; 95% CI, 18 - 34%; p<0.0001). Overall in SOLVD study, in patients with left ventricular dysfunction, <Renitec>reduced

the risk of myocardial infarction by 23% (95% CI, 11 – 34%; p<0.001) and reduced the risk of hospitalization for unstable angina pectoris by 20% (95% CI, 9 – 29%; p<0.001).

There is limited experience of the use in hypertensive pediatric patients >6 years. In a clinical study involving 110 hypertensive pediatric patients 6 to 16 years of age with a body weight ≥20 kg and a glomerular filtration rate >30 ml/min/1.73 m^2, patients who weighed <50 kg received either 0.625, 2.5 or 20 mg of enalapril daily and patients who weighed ≥50 kg received either 1.25, 5 or 40 mg of enalapril daily. Enalapril administration once daily lowered trough blood pressure in a dose-dependent manner. The dose-dependent antihypertensive efficacy of enalapril was consistent across all subgroups (age, Tanner stage, gender, race). However, the lowest doses studied, 0.625 mg and 1.25 mg, corresponding to an average of 0.02 mg/kg once daily, did not appear to offer consistent antihypertensive efficacy. The maximum dose studied was 0.58 mg/kg (up to 40 mg) once daily. The adverse experience profile for pediatric patients is not different from that seen in adult patients.

5.2 Pharmacokinetic properties

Oral enalapril is rapidly absorbed, with peak serum concentrations of enalapril occurring within one hour. Based on urinary recovery, the extent of absorption of enalapril from oral enalapril tablet is approximately 60%. The absorption of oral <Renitec>is not influenced by the presence of food in the gastrointestinal tract.

Following absorption, oral enalapril is rapidly and extensively hydrolyzed to enalaprilat, a potent angiotensin converting enzyme inhibitor. Peak serum concentrations of enalaprilat occur about 4 hours after an oral dose of enalapril tablet. The effective half-life for accumulation of enalaprilat following multiple doses of oral enalapril is 11 hours. In subjects with normal renal function, steady-state serum concentrations of enalaprilat were reached after 4 days of treatment.

Over the range of concentrations which are therapeutically relevant, enalaprilat binding to human plasma proteins does not exceed 60%.

Except for conversion to enalaprilat, there is no evidence for significant metabolism of enalapril.

Excretion of enalaprilat is primarily renal. The principal components in urine are enalaprilat, accounting for about 40% of the dose, and intact enalapril (about 20%).

Renal impairment
The exposure of enalapril and enalaprilat is increased in patients with renal insufficiency. In patients with mild to moderate renal insufficiency (creatinine clearance 40-60 ml/min) steady state AUC of enalaprilat was approximately two-fold higher than in patients with normal renal function after administration of 5 mg once daily. In severe renal impairment (creatinine clearance ≤30 ml/min), AUC was increased approximately 8-fold. The effective half-life of enalaprilat following multiple doses of enalapril maleate is prolonged at this level of renal insufficiency and time to steady state is delayed. (See 4.2 Posology and method of administration.) Enalaprilat may be removed from the general circulation by hemodialysis. The dialysis clearance is 62 ml/min.

Children and adolescents
A multiple dose pharmacokinetic study was conducted in 40 hypertensive male and female pediatric patients aged 2 months to ≤16 years following daily oral administration of 0.07 to 0.14 mg/kg enalapril maleate. There were no major differences in the pharmacokinetics of enalaprilat in children compared with historic data in adults. The data indicate an increase in AUC (normalised to dose per body weight) with increased age; however, an increase in AUC is not observed when data are normalised by body surface area. At steady state, the mean effective half-life for accumulation of enalaprilat was 14 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies suggest that enalapril has no effects on fertility and reproductive performance in rats, and is not teratogenic. In a study in which female rats were dosed prior to mating through gestation, an increased incidence of rat pup deaths occurred during lactation. The compound has been shown to cross the placenta and is secreted in milk. Angiotensin converting enzyme inhibitors, as a class, have been shown to be fetotoxic (causing injury and/or death to the fetus) when given in the second or third trimester.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be implemented nationally]

6.2 Incompatibilities

[To be implemented nationally]

6.3 Shelf life

[To be implemented nationally]

6.4 Special precautions for storage

[To be implemented nationally]

6.5 Nature and contents of container

[See Annex I - to be implemented nationally]

6.6 Instructions for use and handling

[To be implemented nationally]

7. MARKETING AUTHORIZATION HOLDER

[See Annex I -to be implemented nationally]

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

