ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 1220 Wien Austria	Cosaar 12,5 mg - Filmtabletten	12.5 mg	Film-coated tablet	Oral use
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 1220 Wien Austria	Cosaar 50 mg - Filmtabletten	50 mg	Film-coated tablet	Oral use
Austria	Merck Sharp & Dohme GmbH Donau-City-Straße 6 1220 Wien Austria	Cosaar 100 mg - Filmtabletten	100 mg	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 B-1180 Brussels Belgium	COZAAR 100 mg	100 mg	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 B-1180 Brussels Belgium	COZAAR 50 MG	50 mg	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 B-1180 Brussels Belgium	COZAAR 12,5 mg	12.5 mg	Film-coated tablet	Oral use
Belgium	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 B-1180 Brussels Belgium	COZAAR CARDIO START	21 x 12.5 mg + 14 x 50 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Belgium	Therabel Pharma S.A. Rue Egide Van Ophem 108 B-1180 Brussels Belgium	LOORTAN 100 mg	100 mg	Film-coated tablet	Oral use
Belgium	Therabel Pharma S.A. Rue Egide Van Ophem 108 B-1180 Brussels Belgium	LOORTAN 50 mg	50 mg	Film-coated tablet	Oral use
Belgium	Therabel Pharma S.A. Rue Egide Van Ophem 108 B-1180 Brussels Belgium	LOORTAN 12,5 mg	12.5 mg	Film-coated tablet	Oral use
Belgium	Therabel Pharma S.A. Rue Egide Van Ophem 108 B-1180 Brussels Belgium	LOORTAN CARDIO START	21 x 12.5 mg + 14 x 50 mg	Film-coated tablet	Oral use
Bulgaria	Merck Sharp & Dohme Bulgaria EOOD 55 Nikola Vaptzarov blvd. EXPO 2000, east wing, sections B1 & B2, 1st fl. 1407 Sofia Bulgaria	Cozaar	50 mg	Film-coated tablet	Oral use
Cyprus	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem The Netherlands	COZAAR	50 mg	Film-coated tablet	Oral use
Cyprus	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem The Netherlands	COZAAR	100 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem The Netherlands	Cozaar	12.5 mg	Film-coated tablet	Oral use
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem The Netherlands	Cozaar	50 mg	Filmcoated tablet	Oral use
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem The Netherlands	Cozaar	100 mg	Filmcoated tablet	Oral use
Denmark	Merck Sharp & Dohme BV, Postbus 581, 2003 PC, Haarlem The Netherlands	Cozaar Startpakke	12.5 mg + 50 mg	Filmcoated tablet	Oral use
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn Estonia	Cozaar	100 mg	Film-coated tablet	Oral use
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn Estonia	Cozaar	50 mg	Film-coated tablet	Oral use
Estonia	Merck Sharp & Dohme OÜ Peterburi tee 46 11415 Tallinn Estonia	Cozaar 12,5 mg	12.5 mg	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2003 PC HAARLEM the Netherlands	Cozaar	12.5 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2003 PC HAARLEM the Netherlands	Cozaar	12.5 mg + 50 mg	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2003 PC HAARLEM the Netherlands	Cozaar	50 mg	Film-coated tablet	Oral use
Finland	Merck Sharp & Dohme B.V. Waarderweg 39 P.O.Box 581 2003 PC HAARLEM the Netherlands	Cozaar	100 mg	Film-coated tablet	Oral use
France	Merck Sharp Dohme Chibret 3 av. Hoche 75114 Paris Cedex 08 France	Cozaar 100 mg film-coated tablets	100 mg	Film-coated tablet	Oral use
France	Merck Sharp Dohme Chibret 3 av. Hoche 75114 Paris Cedex 08 France	Cozaar 50 mg scored coated tablets	50 mg	Scored coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	CARDOPAL START 12,5 mg Filmtabletten	12.5 mg	Film-coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	LORZAAR 100 mg Filmtabletten	100 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	LORZAAR 50 mg Filmtabletten	50 mg	Film-coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	LORZAAR PROTECT 100 mg Filmtabletten	100 mg	Film-coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	LORZAAR PROTECT 50 mg Filmtabletten	50 mg	Film-coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	LORZAAR START 12,5 mg Filmtabletten	12.5 mg	Film-coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	PINZAAR 100 mg Filmtabletten	100 mg	Film-coated tablet	Oral use
Germany	MSD Chibropharm GmbH Postfach 1202 D-85530 Haar Germany	PINZAAR 50 mg Filmtabletten	50 mg	Film-coated tablet	Oral use
Germany	VARIPHARM ARZNEIMITTEL GmbH Lindenplatz 1 85540, Haar, Germany	LORZAAR VARIPHARMSTART 12,5 mg Filmtabletten	12.5 mg	Film-coated tablet	Oral use
Greece	VIANEX A.E. Tatoiou Street, Nea Erythraia 14671 Greece	COZAAR	12.5 mg	Film-coated tablet	Oral use
Greece	VIANEX A.E. Tatoiou Street, Nea Erythraia 14671 Greece	COZAAR	50 mg	Film-coated tablet	Oral use
Greece	VIANEX A.E. Tatoiou Street, Nea Erythraia 14671 Greece	COZAAR	100 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Hungary	Merck Sharp & Dohme Hungary Ltd 50, Alkotas str. H-1123 Budapest Hungary	Cozaar	12.5 mg	Film-coated tablet	Oral use
Hungary	Merck Sharp & Dohme Hungary Ltd 50, Alkotas str. H-1123 Budapest Hungary	Cozaar	50 mg	Film-coated tablet	Oral use
Hungary	Merck Sharp & Dohme Hungary Ltd 50, Alkotas str. H-1123 Budapest Hungary	Cozaar	100 mg	Film-coated tablet	Oral use
Iceland	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	12.5 mg	Film-coated tablet	Oral use
Iceland	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	50 mg	Film-coated tablet	Oral use
Iceland	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	100 mg	Film-coated tablet	Oral use
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU United Kingdom	COZAAR 50 mg Film-coated Tablets	50 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU United Kingdom	COZAAR 100 mg Film-coated Tablets	100 mg	Film-coated tablet	Oral use
Ireland	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU United Kingdom	COZAAR 12.5mg Film-coated Tablets	12.5mg	Film-coated tablet	Oral use
Italy	Merck Sharp & Dohme (Italia) S.p.A. Via G. Fabbroni 6, 00191 Rome, Italy	LORTAAN 50 mg compresse rivestite con film	50 mg	Film-coated tablet	Oral use
Italy	Merck Sharp & Dohme (Italia) S.p.A. Via G. Fabbroni 6, 00191 Rome, Italy	LORTAAN 12,5 mg compresse rivestite con film	12.5 mg	Film-coated tablet	Oral use
Italy	Merck Sharp & Dohme (Italia) S.p.A. Via G. Fabbroni 6, 00191 Rome, Italy	LORTAAN 100 mg compresse rivestite con film	100 mg	Film-coated tablet	Oral use
Italy	Neopharmed SpA Via G. Fabbroni 6, 00191 Rome, Italy	NEO-LOTAN 50 mg compresse rivestite con film	50 mg	Film-coated tablet	Oral use
Italy	Neopharmed SpA Via G. Fabbroni 6, 00191 Rome, Italy	NEO-LOTAN 12,5 mg compresse rivestite con film	12.5 mg	Film-coated tablet	Oral use
Italy	Neopharmed SpA Via G. Fabbroni 6, 00191 Rome, Italy	NEO-LOTAN 100 mg compresse rivestite con film	100 mg	Film-coated tablet	Oral use
Italy	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.- Viale Shakespeare 47, 00144 Rome Italy	LOSAPREX 50 mg compresse rivestite con film	50 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.- Viale Shakespeare 47, 00144 Rome Italy	LOSAPREX 12,5 mg compresse rivestite con film	12.5 mg	Film-coated tablet	Oral use
Italy	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.- Viale Shakespeare 47, 00144 Rome Italy	LOSAPREX 100 mg compresse rivestite con film	100 mg	Film-coated tablet	Oral use
Latvia	SIA Merck Sharp & Dohme Latvia, Latvija; Skanstes street 13, LV-1013, Riga Latvia	Cozaar 50 mg film-coated tablets	50 mg	Film-coated tablet	Oral use
	SIA Merck Sharp & Dohme Latvia, Latvija; Skanstes street 13, LV-1013, Riga Latvia	Cozaar 100 mg film-coated tablets	100 mg	Film-coated tablet	Oral use
Lithuania	UAB Merck Sharp & Dohme, Geležinio Vilko 18A, LT- 01112 Vilnius Lithuania	Cozaar (Losartan)	12.5 mg	Film-coated tablet	oral use
Lithuania	UAB Merck Sharp & Dohme, Geležinio Vilko 18A, LT- 01112 Vilnius Lithuania	Cozaar (Losartan)	50 mg	Film-coated tablet	oral use
Lithuania	UAB Merck Sharp & Dohme, Geležinio Vilko 18A, LT- 01112 Vilnius Lithuania	Cozaar (Losartan)	100 mg	Film-coated tablet	oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 B-1180 Brussels Belgium	COZAAR 100 mg	100 mg	Film-coated tablet	Oral use
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 B-1180 Brussels Belgium	COZAAR 50 MG	50 mg	Film-coated tablet	Oral use
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 B-1180 Brussels Belgium	COZAAR 12,5 mg	12.5 mg	Film-coated tablet	Oral use
Luxembourg	Merck Sharp & Dohme BV - Chaussée de Waterloo 1135 B-1180 Brussels Belgium	COZAAR CARDIO START	21 x 12.5 mg + 14 x 50 mg	Film-coated tablet	Oral use
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 B-1180 Brussels Belgium	LOORTAN 100 mg	100 mg	Film-coated tablet	Oral use
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 B-1180 Brussels Belgium	LOORTAN 50 mg	50 mg	Film-coated tablet	Oral use
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 B-1180 Brussels Belgium	LOORTAN 12,50 mg	12.5mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Luxembourg	Therabel Pharma S.A. - Rue Egide Van Ophem 108 B-1180 Brussels Belgium	LOORTAN CARDIO START	21 x 12.5 mg + 14 x 50 mg	Film-coated tablet	Oral use
Malta	Merck Sharp & Dohme Ltd., Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom	"Cozaar 100 mg" pilloli miksija b'rita	100mg	Film-coated tablet	Oral use
Malta	Merck Sharp & Dohme Ltd., Hertford Road, Hoddesdon, Hertfordshire EN11 9BU United Kingdom	"Cozaar 50 mg" pilloli miksija b'rita	50mg	Film-coated tablet	Oral use
The Netherlands	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 50	50 mg	Film-coated tablet	Oral use
The Netherlands	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 100	100 mg	Film-coated tablet	Oral use
Norway	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	12.5 mg	Film-coated tablet	Oral use
Norway	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	50 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Norway	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar	100 mg	Film-coated tablet	Oral use
Poland	MSD Polska Sp. z o.o. Chłodna 51 00-867 Warsaw Poland	COZAAR	12.5 mg	Film-coated tablet	Oral use
Poland	MSD Polska Sp. z o.o. Chłodna 51 00-867 Warsaw Poland	COZAAR	50 mg	Film-coated tablet	Oral use
Poland	MSD Polska Sp. z o.o. Chłodna 51 00-867 Warsaw Poland	COZAAR	100 mg	Film-coated tablet	Oral use
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos Portugal	COZAAR	50 mg	Film-coated tablet	Oral use
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos Portugal	COZAAR 100 mg	100 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos Portugal	COZAAR IC	12.5 mg	Film-coated tablet	Oral use
Portugal	Merck Sharp & Dohme, Lda. Quinta da Fonte - Edifício Vasco da Gama, 19 - Porto Salvo P.O. Box 214 2770-192 Paço d' Arcos Portugal	COZAAR IC – Titulação	12.5 mg + 50 mg	Film-coated tablet	Oral use
Portugal	LABORATÓRIO MEDINFAR, Produtos Farmacêuticos, SA Rua Manuel Ribeiro de Pavia, 1-1° Venda Nova 2700-547 Amadora Portugal	LORTAAN IC	12.5 mg	Film-coated tablet	Oral use
Portugal	LABORATÓRIO MEDINFAR, Produtos Farmacêuticos, SA Rua Manuel Ribeiro de Pavia, 1-1° Venda Nova 2700-547 Amadora Portugal	LORTAAN IC- Titulação	12.5 mg + 50 mg	Film-coated tablet	Oral use
Portugal	LABORATÓRIO MEDINFAR, Produtos Farmacêuticos, SA Rua Manuel Ribeiro de Pavia, 1-1° Venda Nova 2700-547 Amadora Portugal	LORTAAN	50 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Portugal	LABORATÓRIO MEDINFAR, Produtos Farmacêuticos, SA Rua Manuel Ribeiro de Pavia, 1-1° Venda Nova 2700-547 Amadora Portugal	LORTAAN 100mg	100 mg	Film-coated tablet	Oral use
Romania	Merck Sharp & Dohme Romania S.R.L. Bucharest Business Park Şos. Bucureşti-Ploieşti, Nr. 1A, Clădirea C1, Etaj 3 Sector 1, Bucureşti Romania	COZAAR, comprimate filmate, 50 mg	50 mg	Film-coated tablet	Oral use
Slovenia	Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana Slovenia	Cozaar 12,5 mg filmsko obložene tablete	12.5 mg	Film-coated tablet	Oral use
Slovenia	Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana Slovenia	Cozaar 50 mg filmsko obložene tablete	50 mg	Film-coated tablet	Oral use
Slovenia	Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana Slovenia	Cozaar 100 mg filmsko obložene tablete	100 mg	Film-coated tablet	Oral use
Spain	MERCK SHARP AND DOHME DE ESPAÑA, S.A. C/ Josefa Valcárcel, 38 28027 Madrid Spain	Cozaar 12.5 mg Inicio	12.5 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Spain	MERCK SHARP AND DOHME DE ESPAÑA, S.A. C/ Josefa Valcárcel, 38 28027 Madrid Spain	Cozaar 50 mg	50 mg	Film-coated tablet	Oral use
Spain	MERCK SHARP AND DOHME DE ESPAÑA, S.A. C/ Josefa Valcárcel, 38 28027 Madrid Spain	Cozaar 100 mg	100 mg	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 12,5 mg filmdragerade tabletter	12.5 mg	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 12,5 mg + 50 mg filmdragerade tabletter	12.5 mg + 50 mg	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 50 mg filmdragerade tabletter	50 mg	Film-coated tablet	Oral use
Sweden	Merck Sharp & Dohme PO Box 581 2003 PC Haarlem The Netherlands	Cozaar 100 mg filmdragerade tabletter	100 mg	Film-coated tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU United Kingdom	COZAAR 50 mg film-coated tablets	50 mg	Film-coated tablet	Oral use

Member State	**Marketing Authorisation Holder**	**Invented name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU United Kingdom	COZAAR 25 mg film-coated tablets	25 mg	Film-coated tablet	Oral use
United Kingdom	Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Herts EN11 9BU United Kingdom	COZAAR 100 mg film-coated tablets	100 mg	Film-coated tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

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

Cozaar (losartan) was included in the list of products for Product Information harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of the Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised SPCs and therefore to harmonise these divergent SPCs across the European Union. Losartan is an orally active angiotensin II (Ang- II) receptor antagonist acting on the AT1 receptor subtype, thus blocking the effect of Ang-II in the renin angiotensin system (RAS) cascade. Losartan is indicated for the treatment of hypertension. Losartan may also delay progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes, hypertension and microalbuminuria (>30 mg/24 hours) or proteinuria (>900 mg/24 hours).

The main areas of disharmony of the existing Summary of Product Characteristics were section 4.1 Therapeutic Indications, section 4.3 Contraindications, and section 4.4 Special Warnings and Precautions for Use.

Therapeutic Indications (SPC section 4.1)

- Treatment of essential hypertension.
The efficacy and safety are well established for the indication “treatment of essential hypertension”. Therefore, the CHMP considered that this is an acceptable indication.

-Reduction in risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy” (“LIFE indication”)”
During the referral procedure, the MAH proposed amending the indication to substitute “cardiovascular morbidity and mortality” with “stroke”. After careful evaluation, the CHMP considered that this indication is acceptable. The LIFE study has been assessed in the past and this has led to the registration of the more extensive indication, i.e. the reduction of the cardiovascular morbidity and mortality (as measured by the combined incidence of CV death, stroke and MI) instead of stroke only. This is the indication currently proposed by the applicant and has been registered in 15 member states of the EU. The reason for this broader indication is that the LIFE study was not a placebo-controlled study, studying the effect on stroke only compared to placebo, but an actively controlled study, comparing a losartan based with an atenolol based antihypertensive treatment using a primary composite endpoint of CV death, stroke and MI. This composite endpoint can be considered as representative for CV morbidity and mortality, and has translated into this indication in many medicinal products that have been discussed in the CHMP (e.g. statins).

At the time of the study, beta-blockade alone, or in combination with diuretics had shown to reduce rates of many CV events by 15-45%. In the LIFE study an additional benefit was noted with regards to stroke for the losartan based strategy, and effects were similar with regard to MI and CV mortality, indicating that the demonstrated beneficial effect of beta-blockade on CV morbidity and mortality in general was also present for losartan.

Since then the beneficial effect of atenolol regarding CV morbidity and mortality has been questioned. A recent review in the BMJ shows that specifically the preventive effect on stroke of atenolol is lower than for other antihypertensives; RR of 1.26 (95%CI: 1.15 to 1.38). As a consequence the observed 25% risk reduction with losartan versus atenolol brings the protective effect of losartan on stroke in the same range as for other antihypertensives.

Therefore, the proposed indication was considered approvable after a majority vote by the CHMP plenum and is supported with the following wording: “reduction of risk of stroke in hypertensive patients with left ventricular hypertrophy, documented by ECG”.

- Renal protection in patients with Type-2 diabetes and proteinuria

The CHMP considered the benefit/risk ratio of this indication is positive. The proposed indication is based on the results from the RENAAL study, where the effect of losartan was investigated on a composite primary endpoint of renal endpoints and mortality in patients with Type II diabetes mellitus with proteinuria. Treatment with losartan, as compared with placebo, resulted in a 16.1% risk reduction in the number of patients reaching the primary composite endpoint. There was also a significant risk reduction for doubling of the serum creatinine and for end-stage renal failure in the patient group treated with losartan. These findings were regarded as clinically relevant for this group of patients. Therefore, the CHMP proposed that the indication should be re-worded to "Treatment of renal disease in patients with hypertension and Type II diabetes mellitus with proteinuria > 0.5g/day as part of an antihypertensive treatment" to reflect the inclusion criteria of the RENAAL study.

- Heart Failure (as second line, when ACE inhibitors are unsuitable).

The CHMP was concerned that the benefit/risk ratio of this indication could not be adequately established. This indication is primarily based on the results of the clinical trials ELITE I and II. The CHMP considered that the data from these trials may not be sufficient to demonstrate the claimed benefit. Whilst the ELITE I indicated an reduction in risk of mortality due to heart failure in patients taking losartan, as compared to captopril, the ELITE II study was not powered to establish equal efficacy between losartan and captopril. Furthermore, the study provided no information on the effect that higher doses of losartan (greater than 50mg) could have on improving efficacy. Importantly, an ongoing study (HEAAL) comparing 50mg with 150mg losartan in patients with heart failure, may give relevant information on the dosing issue and address other open issues such as the negative results observed in patients on beta-blockers and losartan.

After a majority voting at the CHMP plenum, the CHMP recommended that the following wording be proposed to reflect the data from the ELITE I and II studies, within a second-line indication: "Treatment of chronic heart failure (in patients aged 60 or over), when treatment with ACE inhibitors is not considered suitable due to incompatibility or contraindications. Patients with heart failure who have been stabilised with an ACE inihibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction equal to or greater than 40% and should be stabilised under the treatment of the chronic heart failure. The combination of losartan with a beta-blocker should be used with caution".

Contra-indications (SPC section 4.3)

The CHMP considered that the following contra-indications needed to be included in the SPC for Cozaar in all MSs: Pregnancy and lactation; Severely reduced liver function; Angina pectoris; Myocardial infraction; Cerebrovascular disease; Renal artery stenosis; Kidney transplant patients.

Special warnings and precautions for use (SPC section 4.4)

The CHMP considered that the following warnings needed to be included in the SPC for Cozaar in all MSs: Hypersensitivity; Angioedema; Surgery; Anaesthesia; Haemodialysis; Kidney transplant; Black patients; Obstructive valvular disease.

Pregnancy and Lactation

The CHMP considered that the text concerning pregnancy and lactation in the SPC (sections 4.3, 4.4 and 4.6) needed to be amended to include the outcome of the PhVWP report on ACE Inhibitors and angiotensin II receptors antagonists (AIIRAs) and recommendations on the use during the first trimester of pregnancy (EMEA/CHMP/PhVWP/474692/2007). Pregnancy and Lactation should be contraindicated and the appropriate wording included in sections 4.3, 4.4 and 4.6 of the SPC, and the relevant sections of the Package Leaflet.

Use of losartan in children and adolescents

Based on the data submitted during the Article 30 Referral procedure and the outcome of the EU worksharing project assessment of these paediatric data, the CHMP considered that the conclusions of the European Paediatric Worksharing Project on losartan needed to be incorporated into sections 4.2, 4.4, 4.8, 5.1 and 5.2 of Summary of Product Characteristics and the relevant sections of the Package Leaflet.

The following wording has been added to SPC section 4.2 Posology and Method of Administration:

Paediatric hypertension
There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see 5.1: Pharmacodynamic properties). Limited pharmacokinetic data are available in hypertensive children above one month of age (see 5.2 : Pharmacokinetic properties).

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients >20 to <50 kg. In exceptional cases the dose can be increased to a maximum of 50 mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/ kg (or in excess of 100 mg) daily have not been studied in paediatric patients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.

It is not recommended in children with glomerular filtration rate < 30 ml/ min / 1.73 m^2, as no data are available (see also section 4.4).

Losartan is also not recommended in children with hepatic impairment (see also section 4.4).

The following wording has been added to SPC Section 4.4 Special warnings and precautions for use:

Hypotension and Electrolyte/Fluid Imbalance
Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of <COZAAR>, or a lower starting dose should be used (see section 4.2). *This also applies to children.*

Liver Function Impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3and 5.2).
Losartan is also not recommended in children with hepatic impairment (see section 4.2).

Renal Function Impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin angiotensin aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon

discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.
Losartan is not recommended in children with glomerular filtration rate < 30ml/ min/ 1.73 m^2as no data are available (see section 4.2).

Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydratation) likely to impair renal function.
Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

The following wording has been added to SPC Section 4.8 Undesirable effects:

The adverse experience profile for paediatric patients appears to be similar to that seen in adult patients. Data in the paediatric population are limited.

The following wording has been added to SPC Section 5.1.Pharmacodynamic Properties:

<u>Paediatric Hypertension</u>
The antihypertensive effect of Cozaar was established in a clinical study involving 177 hypertensive paediatric 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 weighted >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.
These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mm Hg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

Long-term effects of losartan on growth, puberty and general development have not been studied. The long-term efficacy of antihypertensive therapy with losartan in childhood to reduce cardiovascular morbidity and mortality has also not been established.

The following wording has been added to SPC Section 5.2 Pharmacokinetic properties:

<u>Pharmacokinetics in paediatric patients</u>
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/ kg of losartan (mean doses).
The results showed that the active metabolite is formed from losartan in all age groups.-The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/ toddlers was comparatively high.

The following wording has been added to the Package Leaflet Section 2 Before you take Cozaar:

Use in children and adolescents

<COZAAR> has been studied in children. For more information, talk to your doctor.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling and package leaflet.

- the Summaries of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

- the CHMP concluded that the Marketing Authorisation could be harmonised on the following indications:

  - Treatment of essential hypertension

  - Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria > 0.5 g/day as part of an antihypertensive treatment

  - Reduction of risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (See section 5.1 Life Study, Race)

  - Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility, *especially cough,* or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure

- Pregnancy and Lactation should be contraindicated and the appropriate wording included in sections 4.3, 4.4 and 4.6 of the SPC, and the relevant sections of the Package Leaflet.

- The use of losartan in paediatric patients should be included in sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SPC, and the relevant sections of the Package Leaflet.

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Cozaar and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cozaar and associated names (see Annex I) 12.5 mg film-coated tablets
Cozaar and associated names (see Annex I) 25 mg film-coated tablets
Cozaar and associated names (see Annex I) 50 mg film-coated tablets
Cozaar and associated names (see Annex I) 100 mg film-coated tablets

[To be implemented nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Cozaar 12.5 mg Tablet contains 12.5 mg of losartan (as potassium salt).
Each Cozaar 25 mg Tablet contains 25 mg of losartan (as potassium salt).
Each Cozaar 50 mg Tablet contains 50 mg of losartan (as potassium salt).
Each Cozaar 100 mg Tablet contains 91 100 mg of losartan (as potassium salt).

Each Cozaar 12,5 mg tablet contains 25.5 mg lactose monohydrate.
Each Cozaar 25 mg tablet contains12.75 mg lactose monohydrate.
Each Cozaar 50 mg tablet contains 25.5 mg lactose monohydrate.
Each Cozaar 100 mg tablet contains 51.0 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

[To be implemented nationally]

3. PHARMACEUTICAL FORM

Film-coated tablets

Cozaar 12,5 mg tablet
Blue, oval film-coated tablets marked 11 on one side and plain on the other.

Cozaar 25 mg tablet
White, oval unscored film-coated tablets marked 951 on one side and plain on the other..

Cozaar 50 mg tablet
White, oval film-coated tablets marked 952 on one side and scored on the other.
<The tablet can be divided into equal halves.>

Cozaar 100 mg tablet
White, teardrop-shaped film-coated tablets marked 960 on one side and plain on the other.

[To be implemented nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of essential hypertension.
- Treatment of renal disease in patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.

- Treatment of chronic heart failure (in patients ≥ 60 years), when treatment with ACE inhibitors is not considered suitable due to incompatibility*, especially cough,* or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be stabilised under the treatment of the chronic heart failure.
- Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG (see section 5.1 LIFE study, Race).

4.2 Posology and method of administration

Losartan tablets should be swallowed with a glass of water.
Cozaar may be administered with or without food.

Hypertension
The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning).
Cozaar may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

Pediatric hypertension
There are limited data on the efficacy and safety of losartan in children and adolescents aged 6-16 years old for the treatment of hypertension (see 5.1: Pharmacodynamic properties). Limited pharmacokinetic data are available in hypertensive children above one month of age (see 5.2 : Pharmacokinetic properties).

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients >20 to <50 kg. In exceptional cases the dose can be increased to a maximum of 50 mg once daily. Dosage should be adjusted according to blood pressure response.

In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/ kg (or in excess of 100 mg) daily have not been studied in pediatric patients.

Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.

It is not recommended in children with glomerular filtration rate < 30 ml/ min / 1.73 m^2, as no data are available (see also section 4.4).

Losartan is also not recommended in children with hepatic impairment (see also section 4.4).

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month after initiation of therapy onwards. Cozaar may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Heart Failure
The usual initial dose of Cozaar in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5 mg daily, 25 mg daily, 50 mg daily) to the usual maintenance dose of 50 mg once daily, as tolerated by the patient.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG
The usual starting dose is 50 mg of Cozaar once daily. A low dose of hydrochlorothiazide should be added and/ or the dose of Cozaar should be increased to 100 mg once daily based on blood pressure response.

Use in patients with intravascular volume depletion:
For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered (see section 4.4).

Use in patients with renal impairment and haemodialysis patients:
No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patients with hepatic impairment:
A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment (see sections 4.3 and 4.4).

Use in Elderly
Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 4.4 and 6.1).
2nd and 3rd trimester of pregnancy (see section 4.4 and 4.6)
Lactation (see section 4.6)
Severe hepatic impairment

4.4 Special warnings and precautions for use

Hypersensitivity
Angiooedema. Patients with a history of angiooedema (swelling of the face, lips, throat, and/ or tongue) should be closely monitored (See section 4.8).

Hypotension and Electrolyte/Fluid Imbalance
Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of Cozaar, or a lower starting dose should be used (see section 4.2). This also applies to children.

Electrolyte imbalances
Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with nephropathy, the incidence of hyperkalemia was higher in the group treated with Cozaar as compared to the placebo group (see section 4.8, 'Hypertension and type 2 diabetes with renal disease - Investigations' and 'Post-marketing experience - Investigations' Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a Creatinine Clearance between 30-50 ml/ min should be closely monitored.
The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan is not recommended (see section 4.5).

Liver Function Impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).
Losartan is also not recommended in children with hepatic impairment (see section 4.2).

Renal Function Impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin angiotensin aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Use in pediatric patients with renal function impairment
Losartan is not recommended in children with glomerular filtration rate < 30ml/ min/ 1.73 m^2as no data are available (see section 4.2).
Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.

Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Losartan tablets is not recommended.

Coronary heart disease and cerebrovascular disease
As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure
In patients with heart failure, with or without renal impairment, there is - as with other drugs acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.
There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution (see section 5.1).

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

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

Pregnancy
Losartan should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Other warnings and precautions
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents may increase the hypotensive action of Losartan. Other substances inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: Concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicine (inducer of matabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitantly treatment with fluvastatin (weak inhibitor of CYP2C9).

As with other drugs that block angiotensin II or its effects, concomitant use of other drugs which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with antiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

4.6 Pregnancy and lactation

Pregnancy
The use of losartan is not recommended during the first trimester of pregnancy (see section 4.4). The use of losartan is contra-indicated during the 2nd and 3rd trimester of pregnancy (see section 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk

cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued ARB therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Losartan therapy 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, hyperkalaemia) (see also 5.3 'Preclinical safety data').
Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken losartan should be closely observed for hypotension (see also section 4.3 and 4.4).

Lactation
It is not known whether losartan is excreted in human milk. However, losartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, losartan is contraindicated during breast-feeding (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

4.8 Undesirable effects

The frequency of adverse events listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

In controlled clinical trials for essential hypertension, hypertensive patients with left ventricular hypertrophy, chronic heart failure as well as for hypertension and type 2 diabetes mellitus with renal disease, the most common adverse event was dizziness.

Hypertension
In controlled clinical trials for essential hypertension with losartan the following adverse events were reported

Nervous system disorders:
Common: dizziness, vertigo
Uncommon: somnolence, headache, sleep disorders

Cardiac disorder:
Uncommon: palpitations, angina pectoris

Vascular disorders:
Uncommon: symptomatic hypotension (especially in patients with intravascular volume depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects, rash.

Gastrointestinal disorders:
Uncommon: abdominal pain, obstipation

General disorders and administration site conditions:
Uncommon: asthenia, fatigue, oedema

Hypertensive patients with left ventricular hypertrophy
In a controlled clinical trial in hypertensive patients with left ventricular hypertrophy the following adverse events were reported:

Nervous system disorders:
common: dizziness

Ear and labyrinth disorders:
common: vertigo

General disorders and administration site conditions:
common: asthenia/fatigue

Chronic heart failure

In a controlled clinical trial in patients with cardiac insufficiency the following adverse events were reported:

Nervous system disorders:
uncommon: dizziness, headache
rare: paraesthesia

Cardiac disorders:
rare: syncope, artrial fibrillation, cerebrovascular accident

Vascular disorders:
uncommon: hypotension, including orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
uncommon: dyspnoea

Gastrointestinal disorders:
uncommon: diarrhoea, nausea, vomiting

Skin and subcutanous tissue disorders:
uncommon: urticaria, pruritus, rash

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

Hypertension and type 2 diabetes with renal disease

In a controlled clinical trial in type 2 diabetic patients with proteinuria (RENAAL study, see section 5.1) the most common drug-related adverse events which were reported for losartan are as follows:

Nervous system disorders:
common: dizziness

Vascular disorders:
common: hypotension

General disorders and administration site conditions:
common: asthenia/fatigue

Investigations:
common: hypoglycaemia, hyperkalaemia

The following adverse events occurred more often in patients receiving losartan than placebo:

Blood and lymphatic system disorders:
not known: anaemia

Cardiac disorders:
not known: syncope, palpitations

Vascular disorders:
not known: orthostatic hypotension

Gastrointestinal disorders:
not known: diarrhoea

Muscoskeletal and connective tissue disorders:
not known: back pain

Renal and urinary disorders:
not known: urinary tract infections

General disorders and administration site conditions:
not known: flu-like symptoms

Post-marketing experience

The following adverse events have been reported in post-marketing experience:

Blood and lymphatic system disorders:
not known: Anaemia, thrombocytopenia

Immune system disorders:
rare: hypersensitivity: anaphylactic reactions, angiooedema including swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors; vasculitis, including Henoch-Schonlein purpura.

Nervous system disorders:
not known: migraine

Respiratory, thoracic and mediastinal disorders:
not known: cough

Gastrointestinal disorders:
not known: diarrhoea

Hepatobiliary disorders:
rare: hepatitis
not known: liver function abnormalities

Skin and subcutaneous tissue disorders:
not known: urticaria, pruritus, rash

Muscoskeletal and connective tissue disorders:

not known: myalgia, arthralgia

Renal disorders:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy (see section 4.4)

Investigations:
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan tablets. Elevations of ALT occurred rarely and usually resolved upon discontinuation of therapy. Hyperkalaemia (serum potassium >5.5 mmol/l) occurred in 1.5% of patients in hypertension clinical trials. In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mEq/l and 3.4% of patients treated with placebo (see section 4.4, 'Electrolyte imbalances').

In a controlled clinical trial on patients with cardiac insufficiency, increase in blood urea, serum creatinine and serum potassium has been reported.

The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients. Data in the pediatric population are limited.

4.9 Overdose

Symptoms of intoxication
No experience with overdose in man is available so far. The most likely symptoms, depending on the extent of overdose, are hypotension, tachycardia, possibly bradycardia.

Treatment of intoxication
Measures are depending on the time of drug intake and kind and severity of symptoms. Stabilisation of the circulatory system should be given priority. After oral intake the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary.
Neither Losartan nor the active metabolite can be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Angiotensin II Receptor Antagonists, ATC code: C09CA01

5.1 Pharmacodynamic properties

Losartan is a synthetic oral angiotensin-II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore Losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During administration of Losartan, removal of the angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After discontinuation of Losartan, PRA and angiotensin II values fell within three days to the baseline values.

Both Losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10- to 40- times more active than Losartan on a weight for weight basis.

Hypertension Studies

In controlled clinical studies, once-daily administration of Losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose relative to 5 – 6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70 – 80 % of the effect seen 5-6 hours post-dose.

Discontinuation of Losartan in hypertensive patients did not result in an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, Losartan had no clinically significant effects on heart rate.

Losartan is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.

LIFE-Study
The Losartan Intervention For Endpoint Reduction in Hypertension [LIFE] study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left-ventricular hypertrophy. Patients were randomised to once daily Losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of Losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE-inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.

The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

Race
In the LIFE-Study black patients treated with Losartan had a higher risk of suffering the primary combined endpoint, i.e. a cardiovascular event (e.g. cardiac infarction, cardiovascular death) and especially stroke, than the black patients treated with atenolol. Therefore the results observed with losartan in comparison with atenolol in the LIFE study with regard to cardiovascular morbidity/mortality do not apply for black patients with hypertension and left ventricular hypertrophy.

RENAAL-Study
The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan RENAAL study was a controlled clinical study conducted worldwide in 1513 Type 2 diabetic patients with proteinuria, with or without hypertension. 751 Patients were treated with Losartan
The objective of the study was to demonstrate a nephroprotective effect of Losartan potassium over and above the benefit of a blood lowering pressure.
Patients with proteinuria and a serum creatinine of 1.3 – 3.0 mg/dl were randomised to receive Losartan 50 mg once a day, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE-inhibitors and angiotension II antagonists.
Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72 % of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average).
The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end-stage renal failure (need for dialysis or transplantation) or death.

The results showed that the treatment with Losartan (327 events) as compared with placebo (359 events) resulted in a 16.1 % risk reduction (p = 0.022) in the number of patients reaching the primary composite endpoint. For the following individual and combined components of the primary endpoint, the results showed a significant risk reduction in the group treated with Losartan: 25.3 % risk reduction for doubling of the serum creatinine (p = 0.006); 28.6 % risk reduction for end-stage renal failure (p = 0.002); 19.9 % risk reduction for end-stage renal failure or death (p = 0.009); 21.0 % risk reduction for doubling of serum creatinine or end-stage renal failure (p = 0.01).
All-cause mortality rate was not significantly different between the two treatment groups.
In this study losartan was generally well tolerated, as shown by a therapy discontinuation rate on account of adverse events that was comparable to the placebo group.

ELITE I and ELITE II Study
In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between the patients treated with Losartan and those treated with captopril was observed with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE I Study, that, compared with captopril, Losartan reduced the mortality risk, was not confirmed in the subsequent ELITE II Study, which is described in the following.

In the ELITE II Study Losartan 50 mg once daily (starting dose 12.5 mg, increased to 25 mg, then 50 mg once daily) was compared with captopril 50 mg three times daily (starting dose 12.5 m, increased to 25 mg and then to 50 mg three times daily). The primary endpoint of this prospective study was the all-cause mortality.

In this study 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether Losartan is superior to captopril in reducing all cause mortality. The primary endpoint did not show any statistically significant difference between Losartan and captopril in reducing all-cause mortality.

In both comparator-controlled (not placebo-controlled) clinical studies on patients with heart failure the tolerability of Losartan was superior to that of captopril, measured on the basis of a significantly lower rate of discontinuations of therapy on account of adverse events and a significantly lower frequency of cough.

An increased mortality was observed in ELITE II in the small subgroup (22% of all HF patients) taking beta-blockers at baseline.

Pediatric Hypertension

The antihypertensive effect of Cozaar was established in a clinical study involving 177 hypertensive pediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filration rate > 30 ml/ min/ 1.73 m^2. Patients who weighted >20kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighted > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.

Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.
These results were confirmed during period II of the study where patients were randomized to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mm Hg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.

Long-term effects of losartan on growth, puberty and general development have not been studied. The long-term efficacy of antihypertensive therapy with losartan in childhood to reduce cardiovascular morbidity and mortality has also not been established.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively.

Distribution

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation

About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 mL/min and 50 mL/min, respectively. Renal clearance of losartan and its active metabolite is about 74 mL/min and 26 mL/min, respectively. When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially with a terminal half-life of about 2 hours and 6-9 hours, respectively. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma.

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose/intravenous administration of ^{14}C-labeled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58%/ 50% in the faeces.

Characteristics in Patients

In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.

In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women.

In patients with mild to moderate alcohol-induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers (see section 4.2 and 4.4).

Plasma concentrations of Losartan are not altered in patients with a creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for Losartan is about 2-times higher in haemodialysis dialysis patients.

The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in heamodialysis patients.

Neither Losartan nor the active metabolite can be removed by haemodialysis.

Pharmacokinetics in paediatric patients
The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients > 1 month to < 16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/ kg of losartan (mean doses).
The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/ toddlers was comparatively high.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse effects on the late foetal development, resulting in foetal death and malformations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains the following inactive ingredients:
microcrystalline cellulose (E460)
lactose monohydrate
pregelatinized maize starch
magnesium stearate (E572)
hydroxypropyl cellulose (E463)
hypromellose (E464)

Cozaar 12.5 mg, 25 mg, 50 mg and 100 mg contain potassium in the following amounts: 1.06 mg (0.027 mEq), 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 mEq) respectively.

Cozaar 12.5 mg tablets also may contain carnauba wax E 903, titanium dioxideE171, indigo carmine E132 aluminum lake.

Cozaar 25 mg tablets also may contain Carnauba wax (E903), Titanium dioxide (E171).

Cozaar 50 mg tablets also may contain Carnauba wax (E903), Titanium dioxide (E171).

Cozaar 100 mg tablets also may contain Carnauba wax (E903), Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Cozaar 12.5 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7, 14, 21, 28, 50, 98, 210 or 500 tablets. HDPE bottles of 100 tablets. A package containing 35 tablets (21 pcs of 12.5 mg tablet and 14 pcs of the 50 mg tablet) or 28 tablets (21 pcs of 12.5 mg tablet and **7** pcs of the 50 mg tablet) is available in a PVC/PE/PVDC titration blister package.

Cozaar 25 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7 or 28 tablets.

Cozaar 50 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7, 10, 14, 20, 28, 30, 50, 56, 84, 90, 98, 280 or 500 tablets. HDPE bottles of 100 or 300 tablets. PVC/aluminum foil/nylon blisters with aluminum foil lidding in packs of 10, 14 and 28. A package containing 35 tablets (21 pcs of 12.5 mg tablet and 14 pcs of the 50 mg tablet) or 28 tablets (21 pcs of 12.5 mg tablet and **7** pcs of the 50 mg tablet) is available in a PVC/PE/PVDC titration blister package.

Cozaar 100 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7, 10, 14, 15, 20, 28, 30, 50, 56, 84, 90, 98 or 280 tablets. HDPE bottles of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be implemented nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be implemented nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for Cozaar 12.5 mg blister

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 12.5 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7, 14, 21, 28, 50, 98, 210 or 500 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for Cozaar 12.5 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 12.5 mg film-coated tablets

Losartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally] *[For referral procedures]*

3. EXPIRY DATE

EXP

4. BATCH NUMBER

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for Cozaar 12.5 mg HDPE bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 12.5 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

100 film-coated tablets. See leaflet for further information.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle label for Cozaar 12.5 mg HDPE bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 12.5 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 12.5 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

100 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

N/A

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for Cozaar 25 mg

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 25 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 25 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for Cozaar 25 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 25 mg film-coated tablets

Losartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally] *[For referral procedures]*

3. EXPIRY DATE

EXP

4. BATCH NUMBER

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for Cozaar 50 mg blister

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 50 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7, 10, 14, 20, 28, 30, 50, 56, 84, 90, 98, 280 or 500 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for Cozaar 50 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 50 mg film-coated tablets

Losartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally] *[For referral procedures]*

3. EXPIRY DATE

EXP

4. BATCH NUMBER

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for Cozaar 50 mg HDPE bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 50 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

100 or 300 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle label for Cozaar 50 mg HDPE bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 50 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

100 or 300 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for Cozaar 100 mg blister

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 100 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7, 10, 14, 15, 20, 28, 30, 50, 56, 84, 90, 98, or 280 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister for Cozaar 100 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 100 mg film-coated tablets

Losartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally] *[For referral procedures]*

3. EXPIRY DATE

EXP

4. BATCH NUMBER

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for Cozaar 100 mg HDPE Bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 100 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

100 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Bottle label for Cozaar 100 mg HDPE Bottle

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 100 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

100 tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for Cozaar 12.5 mg and 50 mg (titration package blister)

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 12.5 mg film-coated tablets
Cozaar 50 mg film-coated tablets

Losartan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Cozaar 12.5 mg film-coated mg tablet contains 12.5 mg losartan potassium.
Each Cozaar 50 mg film-coated mg tablet contains 50 mg losartan potassium.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 day initiation pack
Each pack contains a total of 35 tablets:
21 film-coated tablets of 12.5 mg and 14 film-coated tablets of 50 mg losartan potassium.
Each pack contains a total of 28 tablets:
21 film-coated tablets of 12.5 mg and 7 film-coated tablets of 50 mg losartan potassium.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally] *[For referral procedures]*

16. INFORMATION IN BRAILLE

[To be completed nationally] *[For referral procedures]*

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
Trifold
Blister for Cozaar 12.5 mg film-coated tablets
Blister for Cozaar 50 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Cozaar 12.5 mg film-coated tablets
Cozaar 50 mg film-coated tablets

Losartan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

WEEK 1
(day 1-7)
1 tablet = 12,5 mg daily
Use this card first

WEEK 2
(Day 8-14)
2 tablets = 25 mg once daily

WEEK 3
(day 15-21)
1 tablet = 50 mg daily

WEEK 4
(day 22-28)
1 tablet = 50 mg daily

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cozaar
film-coated tablets
losartan potassium

Read all of this leaflet carefully before taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT Cozaar IS AND WHAT IT IS USED FOR

Losartan belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels, causing them to tighten. This results in an increase in blood pressure. Losartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure. Losartan slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes

Cozaar is used

- to treat patients with high blood pressure (hypertension)
- to protect the kidney in hypertensive type 2 diabetic patients with laboratory evidence of impaired renal function and proteinuria ≥ 0.5 g per day (a condition in which urine contains an abnormal amount of protein).
- to treat patients with chronic heart failure when therapy with specific medicines called angiotensin-converting-enzyme inhibitors (ACE inhibitors, medicine used to lower high blood pressure) is not considered suitable by your doctor. If your heart failure has been stabilised with an ACE inhibitor you should not be switched to losartan .
- in patients with high blood pressure and a thickening of the left ventricle, COZAAR has been shown to decrease the risk of stroke (“LIFE indication”).

2. BEFORE YOU TAKE Cozaar

Do not take Cozaar

- if you are allergic (hypersensitive) to losartan or to any of its other ingredients,
- if your liver function is severely impaired,
- if you are, think you may be or are planning to become pregnant (see also “Pregnancy and breast-feeding”),

- if you are breast-feeding.

Take special care with Cozaar

It is important to tell your doctor before taking **Cozaar:**

- if you have had a history of angiooedema (swelling of the face, lips, throat, and/or tongue) (see also section 4 'Possible side effects'),
- if you suffer from excessive vomiting or diarrhoea leading to an extreme loss of fluid and/or salt in your body,
- if you receive diuretics (medicines that increase the amount of water that you pass out through your kidneys) or are under dietary salt restriction leading to an extreme loss of fluid and salt in your body (see section 3 'Dosage in special patient groups'),
- if you are known to have narrowing or blockage of the blood vessels leading to your kidneys or if you have received a kidney transplant recently,
- if your liver function is impaired (see sections 2 "Do not take Losartan" and 3 'Dosage in special patient groups'),
- if you suffer from heart failure with or without renal impairment or concomitant severe life threatening cardiac arrhythmias. Special caution is necessary when you are treated with a ß-blocker concomitantly,
- if you have problems with your heart valves or heart muscle,
- if you suffer from coronary heart disease (caused by a reduced blood flow in the blood vessels of the heart) or from cerebrovascular disease (caused by a reduced blood circulation in the brain),
- if you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland).

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or herbal medicines and natural products.
Take particular care if you are taking the following medicines while under treatment with Cozaar:

- other blood pressure lowering medicines as they may additionally reduce your blood pressure. Blood pressure may also be lowered by one of the following drugs/ class of drugs: tricyclic antidepressants, antipsychotics, baclofene, amifostine,
- medicines which retain potassium or may increase potassium levels (e.g. potassium supplements, potassium-containing salt substitutes or potassium-sparing medicines such as certain diuretics [amiloride, triamteren, spironolactone] or heparine),
- non-steroidal anti-inflammatory drugs such as indomethacin, including cox-2-inhibitors (medicines that reduce inflammation, and can be used to help relieve pain) as they may reduce the blood lowering effect of losartan.

If your kidney function is impaired, the concomitant use of these medicines may lead to a worsening of the kidney function.
Lithium containing medicines should not be taken in combination with losartan without close supervision by your doctor. Special precautionary measures (e.g. blood tests) may be appropriate.

Taking Cozaar with food and drink

Cozaar may be taken with or without food.

Pregnancy and breast-feeding

You should not take losartan in the first 12 weeks of pregnancy, and you must not take them at all after the 13th week as their use during pregnancy may possibly be harmful to the baby.
If you become pregnant while on losartan, tell your doctor immediately. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.
You must not take losartan if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Use in children and adolescents

Cozaar has been studied in children. For more information, talk to your doctor.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed.
Cozaar is unlikely to affect your ability to drive or use machines. However, as with many other medicines used to treat high blood pressure, losartan may cause dizziness or drowsiness in some people. If you experience dizziness or drowsiness, you should consult your doctor before attempting such activities.

Important information about some of the ingredients of Cozaar

Cozaar contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE Cozaar

Always take Cozaar exactly as your doctor has instructed you. Your doctor will decide on the appropriate dose of Cozaar, depending on your condition and whether you are taking other medicines. It is important to continue taking Cozaar for as long as your doctor prescribes it in order to maintain smooth control of your blood pressure.

Patients with High Blood Pressure
Treatment usually starts with 50 mg losartan (one tablet Cozaar 50 mg) once a day. The maximal blood pressure lowering effect should be reached 3-6 weeks after beginning treatment. In some patients the dose may later be increased to 100 mg losartan (two tablets Cozaar 50 mg) once daily
If you have the impression that the effect of losartan is too strong or too weak, please talk to your doctor or pharmacist.

Patients with high blood pressure and type 2 diabetes
Treatment usually starts with 50 mg losartan (one tablet Cozaar 50 mg) once a day. The dose may later be increased to 100 mg losartan (two tablets Cozaar 50 mg) once daily depending on your blood pressure response.

Losartan tablets may be administered with other blood pressure lowering medicines (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used medicines that decrease the level of glucose in the blood (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Patients with Heart Failure
Treatment usually starts with 12.5 mg losartan (one tablet Cozaar 12.5 mg) once a day.

Generally, the dose should be increased weekly step-by-step (i.e., 12.5 mg daily during the first week, 25 mg daily during the second week, 50 mg daily during the third week) up to the usual maintenance dose of 50 mg losartan (one tablet Cozaar 50 mg) once daily, according to your condition.

In the treatment of heart failure, losartan is usually combined with a diuretic (medicine that increases the amount of water that you pass out through your kidneys) and/or digitalis (medicine that helps to make the heart stronger and more efficient) and/or a beta-blocker .

Dosage in special patient groups

The doctor may advise a lower dose, especially when starting treatment in certain patients such as those treated with diuretics in high doses, in patients with liver impairment, or in patients over the age of 75 years. The use of losartan is not recommended in patients with severe hepatic impairment (see section "Do not take losartan").

Administration

The tablets should be swallowed with a glass of water. You should try to take your daily dose at about the same time each day. It is important that you continue to take Cozaar until your doctor tells you otherwise.

If you take more Cozaar than you should

If you accidentally take too many tablets, or a child swallows some, contact your doctor immediately. Symptoms of overdose are low blood pressure, increased heartbeat, possibly decreased heartbeat.

If you forget to take Cozaar

If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten tablet. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cozaar can cause side effects, although not everybody gets them.

If you experience the following, stop taking losartan tablets and tell your doctor immediately or go to the casualty department of your nearest hospital:

A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).

This is a serious but rare side effect, which affects more than 1 out of 10,000 patients but fewer than 1 out of 1,000 patients. You may need urgent medical attention or hospitalisation.

The side effects of medicines are classified as follows:

very common:	happening in more than 1 in 10 patients
common:	happening in 1 in 100 to 1 in 10 patients
uncommon	happening in 1 in 1,000 to 1 in 100 patients
rare:	happening in 1 in 10,000 to 1 in 1,000 patients
very rare:	happening in less than 1 in 10,000 patients
not known	(cannot be estimated from the available data)

The following side effects have been reported with Cozaar:

Common:
- dizziness,
- low blood pressure,
- debility,
- fatigue,
- too less sugar in the blood (hypoglycaemia),
- too much potassium in the blood (hyperkalaemia).

Uncommon:
- somnolence,
- headache,
- sleep disorders,
- feeling of increased heart rate (palpitations),
- severe chest pain (angina pectoris),
- low blood pressure (especially after excessive loss of water from the body within blood vessels e.g. in patients with severe heart failure or under treatment with high dose diuretics),
- dose-related orthostatic effects such as lowering of blood pressure appearing when rising from a lying or sitting position,
- shortness of breath (dyspnoea),
- abdominal pain,
- obstipation,
- diarrhoea,
- nausea,
- vomiting,
- hives (urticaria),
- itching (pruritus),
- rash,
- localised swelling (oedema).

Rare:
- inflammation of blood vessels (vasculitis including Henoch-Schonlein purpura),
- numbness or tingling sensation (paraesthesia),
- fainting (syncope),
- very rapid and irregular heartbeat (artrial fibrillation) brain attack (stroke),
- inflammation of the liver (hepatitis),
- elevated blood alanine aminotransferase (ALT) levels, usually resolved upon discontinuation of treatment.

not known:
- reduced number of red blood cells (anaemia),
- reduced number of thrombocytes,
- migraine,
- cough,
- liver function abnormalities,
- muscle and joint pain,
- changes in kidney function (may be reversible upon discontinuation of treatment) including kidney failure,
- flu-like symptoms,
- increase in blood urea,
- serum creatinine and serum potassium in patients with heart failure,
- back pain and urinary track infection.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE Cozaar

Keep out of the reach and sight of children.

Do not use Cozaar after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store Cozaar in the original package.
Do not open the blister pack until you are ready to take the medicine.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cozaar contains

The active substance is losartan potassium.
Each Cozaar 12.5 mg tablet contains 12.5 mg of losartan potassium.
Each Cozaar 25 mg tablet contains 25 mg of losartan potassium.
Each Cozaar 50 mg tablet contains 50 mg of losartan potassium.
Each Cozaar 100 mg tablet contains 100 mg of losartan potassium.

The other ingredients are microcrystalline cellulose (E460), lactose monohydrate, pregelatinized maize starch, magnesium stearate (E572), hydroxypropyl cellulose (E463), hypromellose (E464).

Cozaar 12.5 mg, 25 mg, 50 mg and 100 mg contain potassium in the following amounts: 1.06 mg (0.027 mEq), 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 mEq) respectively.

The Cozaar 12.5 mg tablets also may contain
carnauba wax (E903), titanium dioxide (E171), indigo carmine (E132) aluminum lake.

The Cozaar 25 mg tablets also may contain Carnauba wax (E903), Titanium dioxide (E171).

The Cozaar 50 mg tablets also may contain Carnauba wax (E903), Titanium dioxide (E171).

The Cozaar 100 mg tablets also may contain Carnauba wax (E903), Titanium dioxide (E171).

What Cozaar looks like and contents of the pack

Cozaar is supplied as unscored film-coated tablets containing 12.5 mg of losartan potassium.

Cozaar is supplied as unscored film-coated tablets containing 25 mg of losartan potassium.

Cozaar is supplied as scored film-coated tablets containing 50 mg of losartan potassium.

Cozaar is supplied as unscored film-coated tablets containing 100 mg of losartan potassium.

Cozaar is supplied in the following pack sizes:

Cozaar 12.5 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7, 14, 21, 28, 50, 98, 210 or 500 tablets. HDPE bottles of 100 tablets. A package containing 35 tablets (21 pcs of 12.5 mg tablet and 14 pcs of the 50 mg tablet) or 28 tablets (21 pcs of 12.5 mg tablet and 7 pcs of the 50 mg tablet) is available in a PVC/PE/PVDC titration blister package.

Cozaar 25 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7 or 28 tablets.

Cozaar 50 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7, 10, 14, 20, 28, 30, 50, 56, 84, 90, 98, 280 or 500 tablets. HDPE bottles of 100 or 300 tablets. PVC/aluminum foil/nylon blisters with aluminum foil lidding in packs of 10, 14 and 28. A package containing 35 tablets (21 pcs of 12.5 mg tablet and 14 pcs of the 50 mg tablet) or 28 tablets (21 pcs of 12.5 mg tablet and **7** pcs of the 50 mg tablet) is available in a PVC/PE/PVDC titration blister package.

Cozaar 100 mg - PVC/PE/PVDC blister packages with aluminum foil lidding in packs of 7, 10, 14, 15, 20, 28, 30, 50, 56, 90, 98 or 280 tablets. HDPE bottles of 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

<To be completed nationally> <To be completed nationally>

This medicinal product is authorized in the Member States of the EEA under the following names:

Member State	**Invented name**
Austria	Cosaar 12,5 mg - Filmtabletten
Austria	Cosaar 50 mg - Filmtabletten
Austria	Cosaar 100 mg - Filmtabletten
Belgium	COZAAR 100 mg
Belgium	COZAAR 50 MG
Belgium	COZAAR 12,5 mg
Belgium	COZAAR CARDIO START
Belgium	LOORTAN 100 mg
Belgium	LOORTAN 50 mg
Belgium	LOORTAN 12,50 mg
Belgium	LOORTAN CARDIO START
Bulgaria	Cozaar
Cyprus	COZAAR
Denmark	Cozaar, Cozaar Startpakke
Estonia	Cozaar, Cozaar 12,5 mg
Finland	Cozaar
France	Cozaar 100 mg film-coated tablets
France	Cozaar 50 mg scored coated tablets
Germany	CARDOPAL START 12,5 mg Filmtabletten
Germany	LORZAAR 100 mg Filmtabletten
Germany	LORZAAR 50 mg Filmtabletten
Germany	LORZAAR PROTECT 100 mg Filmtabletten
Germany	LORZAAR PROTECT 50 mg Filmtabletten
Germany	LORZAAR START 12,5 mg Filmtabletten

Germany	PINZAAR 100 mg Filmtabletten
Germany	PINZAAR 50 mg Filmtabletten
Germany	LORZAAR VARIPHARMSTART 12,5 mg Filmtabletten
Greece	COZAAR
Hungary	Cozaar
Ireland	COZAAR 50 mg Film-coated Tablets
Ireland	COZAAR 100 mg Film-coated Tablets
Ireland	COZAAR 12.5mg Film-coated Tablets
Italy	LORTAAN 50 mg compresse rivestite con film
Italy	LORTAAN 12,5 mg compresse rivestite con film
Italy	LORTAAN 100 mg compresse rivestite con film
Italy	NEO-LOTAN 50 mg compresse rivestite con film
Italy	NEO-LOTAN 12,5 mg compresse rivestite con film
Italy	NEO-LOTAN 100 mg compresse rivestite con film
Italy	LOSAPREX 50 mg compresse rivestite con film
Italy	LOSAPREX 12,5 mg compresse rivestite con film
Italy	LOSAPREX 100 mg compresse rivestite con film
Latvia	Cozaar 50 mg film-coated tablets
Latvia	Cozaar 100 mg film-coated tablets
Lithuania	Cozaar (Losartan)
Luxembourg	COZAAR 100 mg
Luxembourg	COZAAR 50 MG
Luxembourg	COZAAR 12,5 mg
Luxembourg	COZAAR CARDIO START
Luxembourg	LOORTAN 100 mg
Luxembourg	LOORTAN 50 mg
Luxembourg	LOORTAN 12,50 mg
Luxembourg	LOORTAN CARDIO START
Malta	"Cozaar 100 mg" pilloli miksija b’rita
Malta	"Cozaar 50 mg" pilloli miksija b’rita
Netherlands	Cozaar 50
Netherlands	Cozaar 100
Poland	COZAAR
Portugal	COZAAR
Portugal	COZAAR 100 mg
Portugal	COZAAR IC
Portugal	COZAAR IC – Titulação
Portugal	LORTAAN IC
Portugal	LORTAAN IC- Titulação
Portugal	LORTAAN
Portugal	LORTAAN 100mg
Romania	COZAAR, comprimate filmate, 50 mg
Slovenia	Cozaar 12,5 mg filmsko obložene tablete
Slovenia	Cozaar 50 mg filmsko obložene tablete
Slovenia	Cozaar 100 mg filmsko obložene tablete
Spain	Cozaar 12,5 mg Inicio
Spain	Cozaar 50 mg

Spain	Cozaar 100 mg
Sweden	Cozaar 12,5 mg filmdragerade tabletter
Sweden	Cozaar 12,5 mg + 50 mg filmdragerade tabletter
Sweden	Cozaar 50 mg filmdragerade tabletter
Sweden	Cozaar 100 mg filmdragerade tabletter
United Kingdom	COZAAR 50 MG FILM-COATED TABLETS
United Kingdom	COZAAR 25 MG FILM-COATED TABLETS
United Kingdom	COZAAR 100MG FILM-COATED TABLETS
Iceland	Cozaar
Norway	Cozaar

This leaflet was last approved in